SERUM SICKNESS

AUS DER K. K. UNIVERSITÄTS-KINDER-KLINIK
IN WIEN.
(VORSTAND PROF. ESCHERICH.)

DIE
SERUMKRANKHEIT

VON

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LEIPZIG UND WIEN.
FRANZ DEUTICKE
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SERUM SICKNESS

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To
Catherine

PREFACE TO THE ENGLISH TRANSLATION

Since the original publication of the *Serum Sickness*, 45 years have elapsed It took a long time before the medical world realized the fundamental value of these studies What is now called *Allergy* is based on observations published in this book However *von Pirquet* did not coin the term *Allergy* until 1906

During the last two decades many physicians have tried to acquire a copy of the original edition of *Die Serumkrankheit* It became more and more difficult to obtain a copy Furthermore the English speaking physicians experienced difficulties in getting correct information from the book written in German I was frequently asked where one might borrow a copy of the Serum Sickness book I often thought that it would be advisable to translate the book into English but I hesitated to do it, because translations are difficult and time consuming Such time could better be used for an original work It was not until the publishing firm, The Williams and *Wilkins Company, approached me with the request for a translation that* I consented to do it, influenced by the belief that I owed it to my dear friend *von Pirquet* that I should translate this work

Thus it is now accomplished and I have the hope that it will assist in the clarification of the fundamental work upon which was founded *Allergy* and that it will shed light upon the greatness of *Pirquet* who was, all the time these studies were made, completely aware of all the ramifications that would arise from these basic observations

It is a great satisfaction to me and was likewise to *Pirquet* during his life that not only were the clinical observations complete but also that the theoretical ideas stood the test of time

The theory that the interaction between antigen and antibody is responsible for the onset and course of serum sickness is still the theory best suited for its explanation That the breaking down of foreign protein by enzymatic (digestive) substances produces the toxic phase is still accepted It must be stressed that the existence and behavior of the incubation time gave the key which opened the secret lock on the closet where the solution of so many extremely interesting and important problems lay hidden

Many other problems mentioned in *Serum Sickness* were later elaborated by *Pirquet*, see vaccination, measles, tuberculosis, etc It is not necessary for me to say that *Pirquet* is really the father of all skin testing The tuberculin test is a logical evolution of the ideas of the genius, *Pirquet* All our allergy tests and almost everything what we know about allergic diseases have their origin in the observations in serum sickness which contain passive transfer and serum sickness in "reverse"

For some time I had the intention to combine a translation of *Serum Sickness* with discussions concerning the progress which has been attained during the 45 years since its publication It would have been a very difficult task because several thousand publications have appeared Here it is impossible to report the evolution of allergy in greater detail I wish merely to mention some other concepts concerning the theory of allergy and hyperergic (anaphylactic) reaction One of these concepts advocated by French investigators (Villaret, Vallery Radot and others) is to the effect that the symptoms of allergy may depend upon an excess of acetylcholin or upon some disturbance in its normal breakdown by the cholin esterase *Urbach* contends that acetycholine and similar substances are formed as the end results and not immediately by the interaction of antigen and antibody Endotoxin and proteictoxin may likewise liberate or produce these substances from the cells Histamine may be one of the proteictoxins arising during the antigen antibody interaction but not the only one However histamine may be also liberated from the cells through the irritating effect of other substances produced by the antigen antibody interaction The histamine theory led to the use of anti histamine drugs (Benadryl, and Pyribenzamine, etc) which have been especially effective against hives Lately they are also used against "allergic colds' Histamine cannot sufficiently explain all allergic reactions

Doerr is the outstanding champion of the "physical" theory as the basis of anaphylactic shock He assumes that the antigens and antibodies, substances of high molecular weight react on the cell membrane but do not penetrate it The consequence is that physico chemical changes are instituted which act as an irritant to the cells According to *Bronfenbrenner* the interaction between antigen antibody serves to disturb the delicate adjustment of colloidal conditions existing in the serum as well as at the surface of the tissue cells *Widal* looks upon anaphylactic shock as representing a disturbance of the colloidal balance He and his school designate the changes of the colloids in the blood as "hemoclastic crisis" and those in the tissues as "colloidoclasia" *Lumière*, on the contrary, explains the nature of anaphylactic (hyperergic) phenomena on the basis of invisible flocculation occurring in the blood stream of allergic individuals as the encounter between antigen and serum antibody These various theories may have an important meaning in explaining anaphylactic (hyperergic) shock, but cannot be used as an explanation of all allergic phenomena In almost all of the theories the interaction between antigen and antibody plays a prominent role

Landsteiner made an outstanding contribution to chemical allergy when he demonstrated the attachment of simple chemical compounds to the protein of the organism, creating in this way an antigen (*Forssman* antigen)

There are numerous publications which are helpful to physicians in their study of the later phases in the development of allergy

COOKE R A Allergy in Theory and practice W B Saunders Company 1947
DOERR R Arch Derm & Syphilol 181 7 1926
——— Allergic Phenomena Handbook of Normal and Path Physiology 13 650 1929
——— Allergy and Anaphylaxy Hdb Path Microorg ad3 1 part 2 759 1929
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PIRQUET v Allergy Erg Inn Med & Kind I 420 1908 and V 459 1910
——— Klinische Studien ueber Vaccinat on und vaccinale Allergie Mü Med W 53 457 1906
RICH A R AND GREGORY T E Experimental demonstration that periarteritis nodosa is a man festation of hypersensit vity Bull Johns Hopkins Hosp 72 65 1943
——— ——— Experimental evidence that lesions with the bas c characteristics of rheumatic carditis can result from anaphylactic hypersensitivity Bull *Johns Hopkins Hosp 73 239 1943*
——— Role of hypersensitivity in periarteritis nodosa etc Bull Johns Hopkins Hosp 71 123 1942
SCHICK B Allergy and immunity Jour Mt S nai Hosp XIV 3 1947
URBACH AND GOTTLIEB Allergy Grune and Stratton New York 1943 and 1948 (With over 2260 references)

CONTENTS

INTRODUCTION

The introduction of foreign blood and foreign protein in a way other than through the gastrointestinal tract is nothing new Particularly transfusions, consisting of the transmission of blood of one individual into the circulation of another individual, were used as a therapeutic measure for some time Originally the most varied diseases were treated with this method It can be stated with certainty that the first direct and successful transfusion was carried out with lamb blood on June 15, 1667 by *Denis*, quoted by Landois in an article on Transfusion in Eulenberg Realencyclopedia 3rd Edition

These transfusions with lamb blood seem to have given no outstanding results As early as 1691 Jungker said that he could not obtain satisfactory effects and in 1763 Heister found that "unfortunately only a few patients experienced the expected help and very much noise was made in the beginning, but at present one hears very little of it'

At the beginning of the last century experiments with transfusion of lamb blood were again made As prominent indications, acute anemia and poisoning were mentioned These intravenous injections of lamb blood were soon found to be very dangerous Frequently high fever up to 106° was observed half an hour after the injection Also embolic symptoms, hemorrhages, and hemoglobinuria called for caution The cause of these complications and the whole scientific basis of the doctrine of transfusions were discussed and partly clarified only in 1873 by Landois and by Ponfick in 1875 These authors pointed out that the blood cells of animals are dissolved in the circulating blood of the recipient Naunyn and Francken showed that coagulation occurs if one brings dissolved hemoglobin into the circulation Many leukocytes are destroyed by the dissolved hemoglobin Thus generators of fibrin are set free, creating fibrin Through extensive coagulation death may be caused by asphyxia

We do nothing further than mention these symptoms appearing immediately after transfusions of foreign blood, because they have nothing to do with serum disease as such Of much more interest to our problem is the fact that as early as about 1870 observers noted urticaria eruptions several days after the transfusion Dallera (Considerazioni e casi clinici di transfusion del sangue, Il Morgagni disp , 7: 1874) reported that a female patient suffering with "hysteric mania" broke out with an urticaria eruption all over her body ten days after a transfusion On that day her blood still contained the injected red cells of the animal

Neudoerfer (Contributions to Blood Transfusions, Zeitschr f Chir, Bd 6) noted that urticaria frequently appeared after a blood transfusion Landois also saw eruptions of urticaria after transfusions

On account of the severe damage caused by tranfusions of lamb blood, transfusions of animal blood have been almost entirely given up and we do not expect that the newly performed experiments of Dominici (Wr Med Woch, 1895) will revive the use of lamb blood

After lamb blood transfusions milk transfusions were tried for a while, particularly in England This therapy soon disappeared The final opinion of that time is best expressed by the words of Montard, Martin and Richet who say (Injections intravenouses de lait et de sucre, Soc de Biol, 26 7, 1879) 'As therapy milk transfusion is useless and dangerous and should therefore be absolutely condemned' Also the subcutaneous and intra peritoneal injection of blood and milk did not find any followers

After the lamb blood tranfusions had been more and more replaced by infusions with sodium chloride and by transfusions with defibrinated human blood there was no reason to discuss further the danger and disadvantages of transfusion of foreign blood or serum The method and its danger were forgotten

The situation changed in 1894 with the rapidly increasing use of diphtheria antitoxin, which was prepared by the immunization of horses with diphtheria toxin Neither red cells nor fibrin were injected Furthermore the injections were made subcutaneously rather than intravenously and the amount of the injected foreign protein was much smaller This was the reason why, in the majority of cases, no bad effect was noted

Lublinski (An After Effect of Antitoxin in Treatment of Diphtheria," Deutsch Med Wo, 1894 45. 1847) was the first to publish a case describing a rash after injection of diphtheria serum As the title of the publication indicates, Lublinski thought that the symptoms were due to the antitoxin content of the serum

On the second and third day of the disease an eight year old girl received three doses of 10 cc Behring s diphtheria antitoxin On the fifth day a red inflammatory halo appeared around the site of injection Nine days after the last injection multiple and very painful swellings of the joints developed accompanied by high temperature and a macular rash resembling an erythema exsudativum multiforme The intensive symptoms lasted four days With the disappearance of the rash pain and swelling of the joints receded

In the very next issue of the Deutsche Medizinische Wockenschrift, *Scholz* described similar symptoms in two children and in a physician who developed urticaria after a prophylactic injection The wife of the physician, also injected, suffered intensive pain in many joints

Succeeding authors were *Cnyrim*,[1] *Asch*,[2] *Rembold*,[3] and *Treymann*[4] At this time a great number of publications appeared in rapid succession, which made it more and more certain that the unpleasant symptoms due to diphtheria serum were relatively insignificant One became accustomed to accept them without further ado Thus almost every publication concerned with diphtheria serum ended with the mention of the occurrence of rashes and other annoying conditions As far as the cause of these symptoms was concerned, the opinion was frequently expressed that the serum may contain toxic substances At that time *Heubner* and *Bokay* expressed their suspicion that serum rashes may be due to substances in the serum of the animal different from the antitoxin *Johannesen proved experimentally that the agents in the horse serum which produces the sickness must be the horse serum itself, i e the foreign protein*, as the same symptoms were seen in persons not suffering from diphtheria who were injected with normal horse serum In twenty-two individuals fever developed eight times, skin rashes twelve times

Sévestre (Soc Med des Hopitaux, 31. 8, 196) thought that only those rashes which appeared between eight and ten days after injection were due to the serum itself The later symptoms, particularly the morbilli-like rashes accompanied by high temperature, he thought were the effect of a streptococci infection However, even at that time *Neter* disagreed with him in the discussion, stating that also the last mentioned symptoms are due to the serum, as he saw the same symptoms when he used horse serum in cases of pneumonia and tuberculosis Sévestre s theory is at present supported only by *Marfan* (Soc Méd Hôp, 24: 3, '05), whereas we and all other authors share the opinion of Johannesen and Neter *Monti*, who at first agreed with Sévestre, retracted this opinion after he saw the same symptoms follow an injection of pure and sterile horse serum Almost all authors agreed that the damage due to serum injections was, as a whole, small This opinion prevailed in spite of the fact that from time to time severe cases of sickness and even death occurred in connection with serum injections *Gottstein* (Ther Monatsh, 5· 96) published, besides the famous Langerhans case, eight deaths in diphtheria patients and four deaths among other patients Since this publication only a few fatal cases have been reported Subjected to a critical examination, all these fatal cases may be differently explained These observations were not allowed to interfere with the victorious extension of the use of diphtheria antitoxin

[1] Deutsche med Woch Nr 48 1894

[2] Berl klin Woch Nr 51 1894

[3] Deutsche med Woch 51 1894

[4] A case of acute hemorrhagic Nephritis following the use of diphtheria-serum of Behring However, this case was not accepted by the critic

Among all of the symptoms following serum injections, the occurrence of rashes was so prevalent that all symptoms were named *Serumexanthema*

Knowledge about serum exanthema was greatly advanced by the publications of *Hartung* (Serum Exanthema, in Diphtheria Jahrb f Kinderh, 1896, 72) and *Daut* (Statistics of Serum Exanthema, Jahrb f Kinderh, Bd 44, 1897, 289) These publications appertained to the individual symptoms and their frequency At first *Hartung* gave a complete survey of the literature to date From the statistics of the Kaiserl Gesundheitsamt he collected 4358 cases of serum injections and from other statistics 2661 cases Exanthema occurred in 8 1% and 11 4% respectively of the cases He concluded that the frequency depends principally upon the serial numbers (that is upon the individual differences of the horses) and not upon the amount of the injected serum nor upon the amount of antitoxin Hartung discusses the period of the incubation time extensively Its duration also seems to depend upon the sort of serum used He does not try to explain the incubation period He divides the exanthemata into different groups and thoroughly discusses a number of other symptoms

Daut arrives at similar results He describes 38 cases of serum exanthemata in 339 cases injected He too observed that certain kinds of serum produced rashes more frequently than did other kinds He stresses the general scientific importance of the symptoms of serum exanthema Both authors point out the peculiar fact that these symptoms preferably appear on certain so-called critical days It was ascertained that the symptoms of serum exanthema showed increasing intensity with increasing amounts of serum injected This observation was taken into consideration in the manufacture of diphtheria serum, since it was desired to attempt an increase in the concentration of the antitoxin of the serum Furthermore after *Bujwid* called attention to the toxicity of fresh horse serum, it was recommended that only serum stored for a longer period should be used for therapeutic measures From now on the frequency of rashes after serum injection decreased perceptibly But at the same time the interest of physicians in these symptoms lessened before the cause of the symptoms were sufficiently understood Only occasionally did publications about serum exanthema appear, and then they were most frequently for the purpose of discussing their significance in the differential diagnosis of scarlet fever and measles

In 1902 *Ritter von Rittershain* wrote (Jahrb f Kind, vol 55) as the first sentence of his conclusions "The serum exanthemata occur not only less frequently (6 45% against 22% in 1897) but have become in every respect less harmful" The same author reports 1221 cases of diphtheria patients injected with serum and agrees in the main with the findings of Hartung and Daut He remarks especially about the difficulty of differentiating scarlatiniform rashes of serum exanthema from scarlet fever rashes Only in the last years has more attention been paid to serum symptoms

This is due to the fact that serum therapy has been extended to other diseases (sepsis, rheumatism, dysentery, scarletfever), in the treatment of which larger doses of serum were usually used Furthermore, biological research made it possible for us to investigate the fate of the injected serum and, to a certain extent, to study the changes which developed in the injected organism

F Hamburger and *Moro* showed (Wiener klin Wo, 1903, Nr 15) that not only animals but also human beings produce precipitins after an injection of foreign serum F Hamburger studied in a further work (*Arteigenheit und Assimilation, Wien, Deuticke, 1903) the great difference be*tween parenteral and enteral introduction of foreign protein He tried to explain why the foreign protein is assimilated if taken by the normal physiological route, whereas if introduced in the phylogenetically abnormal way of parenteral injection, it produced antibodies and reactions in the form of disease

Von Dungern (The Antibodies, Jena, Verlag Fischer, 1903), *Arthus* (Comptes rendus de la Soc de biol, **20. 6**, 1903), *Kraus* and *Levaditi* (Comptes rendus de l'academie des sciences, **5:** IV, 4, 1903) and we were able to use animal experimentation in order to get an insight into the changes in the organism after serum injection As far as the symptoms in human beings are concerned the department of Scarlet Fever and Diphtheria in the St Anna Children's Hopital gave us ample material for the study of serum exanthema The variety of the symptoms, which nevertheless belong all to one disease entity, deserves renewed interest, particularly as the disease has findings which are very valuable for pathology as a whole

Besides the possibility of following the fate of the injected serum and the reaction of the organism to it, we have, in the study of this disease, the further advantage that we are able to vary voluntarily the amount of the pathogenic agents We have abandoned the expression "serum exanthema" (Zur Theorie der Inkubationszeit, Wiener klin Wo, 1903, Nr 45) because we think that this name could easily lead to the idea that the rash was the most important symptom of the disease, in its place we have proposed the name "serum disease" or "*serumsickness*" For justification of this change we shall bring proof

Francioni has already accepted this name in his last publication (La Malattia da Siero, Archivio di Biologia normale e patologia, Bd 58 Sept Okt, 1904)

We are very grateful to our revered chief, Prof *Escherich*, and also to Doz *Moser* for their great interest in the progress of our study We also thank Drs J *Hertzka*, E *Lazar*, E *Fromm*, and v *Reuss* for their help in some of the investigations

Vienna June 1905

CHAPTER I

CLINICAL ASPECTS OF SERUM SICKNESS

GENERAL CLINICAL PICTURE

Subcutaneus injection of serum produces smaller or larger swelling according to the amount of serum injected. The absorption takes more time than the absorption of the same amount of a physiological NaCl solution, because the serum is more viscous. But even 200 cc of serum are completely absorbed after 24 to 48 hours As a rule no other changes can be observed than local tenderness During the following days the site of injection does not show any reaction, the general wellbeing is not disturbed. Nothing points to the fact that a foreign substance is present in the system, which will lead to disease Most frequently the symptoms of disease start suddenly between 8 and 12 days after the injection.

Only occasionally may prodromal symtoms be found several days preceding the real onset of the disease. The skin is sensitive to slight irritation. Indistinct redness is seen at the site of the injection. The neighborhood is a little red and itches The most constant prodromal symptom is a slight swelling of the regional lymph nodes

At this time the disease proper starts with an eruption of skin manifestations which almost always belong to the urticaria group Generally they are at first seen at the site of the injection and its neighborhood The rash spreads rapidly over the body and is frequently found at the same time in symmetrical regions The erupting hives are partly pale, partly surrounded by a red halo, the latter is seen particularly if the patient scratches a great deal. If the eruption of hives is very dense they may become confluent, then the whole environment appears infiltrated by edema The edema may disfigure the face The intensive itching makes the patient restless and unhappy

All eruptions disappear quickly, the single urtica lasting only several hours, the whole eruption of hives rarely longer than 2 to 3 days A regular sequence in the further development of the rash, as in smallpox or measles, can not be seen.

Meanwhile the temperature has risen to a more or less high figure, being a sign of the participation of the rest of the organism. The sensorium however is free, the pulse corresponds to the temperature, the quality of the pulse is good. Besides this sequence of symptoms which makes the name "serum exanthema' as a designation of the symptom complex plausible, other symptoms appear We have already mentioned that the lymph nodes, regional to the site of the injection, become larger during the

period of incubation This swelling increases rapidly with the onset of the temperature and the rash and may later spread to other lymph glands of the organism The swelling is painful with or without pressure The lymph nodes become smaller after the other symptoms of the disease have passed the height of their intensity The decreasing glandular swelling is, therefore, a valuable prognostic symptom, indicating that the end of the serum sickness is approaching The behavior of the kidney function and the appearance of edema deserve special attention The latter is almost always present as a typical symptom The edema is not only visible but can be objectively determined by taking the body weight daily, a method for the determination of edema inaugurated by Pirquet in nephritis With the onset of the disease the curve of the body weight rises in spite of fever and diminished intake of food The maximum of the weight curve coincides, as a rule, with the maximum of the symptoms of the disease If the edema reaches a certain intensity it can be seen with the naked eye or demonstrated by pressure with the finger In its localization, the edema resembles more or less the nephritic edema However as there are usually no abnormal findings in the urine, even in cases of intensive edema, nothing indicates an involvement of the kidney Only in the minority of cases is albumen found in the urine several days after the onset of edema The amount of albumen is always small Never was it more than $\frac{1}{4}$ pro mille The sediment is scarce Most frequently one finds only a few hyaline casts and some red blood corpuscles The amount of urine is less at the time of the rise in weight but never reaches anuria

Whereas the symptoms mentioned are constant all other symptoms are less frequent Only the joint pain should be mentioned which due to its injury to the patient's general well-being was noticed from the beginning as one of the most striking symptoms We shall deal later in special chapters with the variety of rashes, with the seldom observed symptoms on the mucous membrane and with the blood findings

When the disease is of short duration the general well being is usually little disturbed and indeed is in marked contrast to the frequently high fever However there are cases which, after an injection of a large amount of serum, lasted four to five weeks In such cases severe prostration and intensive emaciation may ensue At the end of the disease convalescence sets in and with a rapid increase of weight, all symptoms of the sickness disappear No after effects are observed and one of the individual symptoms lead to a permanent damage A fatality for which the serum could be considered the cause we never saw At most it might be considered whether or not, in an originally serious disease, where serum treatment is necessary, the last remnant of resistance may not have been destroyed by the addition of the serum sickness

A description of the general picture of serum sickness affords great difficulty not only because of the changing forms of the symptoms, but also because of the dependence of the intensity of the disease upon individual differences on the one side and on the other hand upon the kind and amount of the serum injected Cases of serum sickness which are from a practical point of view the most important because they occur most frequently, are cases of a rudimentary character showing only one or another symptom, most often fever and a rash The following two cases constitute an illustration that the same serum given in the same amount with the same family disposition—with siblings—has as a result similar symptoms

G Leopold 10 years admitted on 12/9/03 on account of Pharynx Diphtheria On 12/9 1000 Antitoxin units (8 cc) Diphtheria serum On 12/13 the membranes

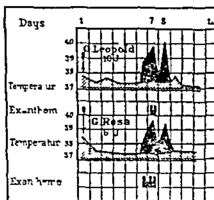


CHART I

in the pharynx had already disappeared During the first 5 days the child had no fever

On the 6th day rise in temperature to 39.8°C Pain in the shoulder joints Aspirin 0 5 g without influence On the 7th day after the recent rise in temperature to over 40°C an eruption of urticaria appeared around the site of the injection Pain in the shoulder joints diminishing Eighth day after a remission of the fever to 3[illegible] in the morning a sudden rise in temperature to 40° After that no further symptoms (Chart I)

On the chart the temperature induced by serum sickness is marked as a black field

G Rosa 6-year old sister of Leopold also admitted with Pharynx Diphtheria

[illegible] the 6th day

In axilla no lymph nodes that could be felt, in the groins they were lentil-sized On the 9th day 37 3°–37.2° temperature On that night eruption of generalized urticaria with bright red halo, intensive itching appeared, otherwise patient lively

inguine pea-sized

11th day Yesterday afternoon and evening intensive eruption of hives Edema can be elicited by pressure with the finger Patient gained since the first weighing almost one kg, since yesterday about 350 g

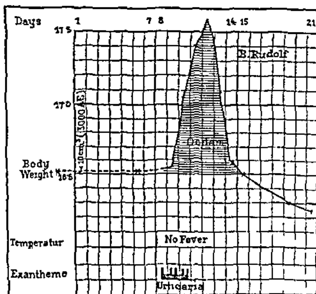


Chart II

12th day Skin pale, edema still increasing

13th day Edema receding

14th day Quick disappearance of edema Large amount of urine Skin pale No edema discernible

In Stephan Th the symptoms of serum sickness, which consisted of a morbillous rash, fever, enlarged spleen, lasted 8 days

Admitted with diphtheritic croup on 12/26/02 Injection of 1500 A U (8 cc) Diphtheria serum On the 8th day after injection slight rise in temperature without a rash On the 12th day with higher temperature there appeared morbillous eruptions over the whole body Temperature up to 39.5° *Spleen distinctly enlarged 2 fingers* breadth below the costal margin

On the 13th and 14th day *post injectionem*, repeated morbillous eruptions with temperature above 39° Only on the 17th day after injection free from fever

For the study of serum sickness it is advisable not to use the more common, rudimentary forms, but rather cases with well-developed characteristic symptoms Therefore, although we describe mostly serious cases as paradigma, it should not be concluded that such cases are the rule We selected intensive cases from a great number of milder cases in order to present special symptoms in their most characteristic form Between mild and severe cases there exist cases of all degrees of intensity The table on page 11 gives a summary of the most important symptoms in their grouping and varied intensity

In Chart III, five cases of serum sickness after injection of 100 to 200 cc of horse serum are depicted in such a way that the day of injection is shown as the first day on the chart The black field shows the fever due to the serum sickness The temperature of the original disease (treated with serum) is shown as plain line We see an almost simultaneous onset of fever after an incubation of 8 to 9 days But after that an entirely different course of the fever is seen The duration of the fever fluctuated between one week (Case 2) three weeks (Case 5), the intensity of fever between 37 5° (Case 1) and 40 2° (Case 5) In a similar way we also see a different distribution of rashes edema, joint pain, lymph gland swelling and albuminuria

A rather exhaustive picture of all symptoms is shown in the following case

Karl L, 4 years, admitted on 11/9/03 On 11/11, 80 cc scarlet fever serum were injected subcutaneously into the right lower side of the abdomen The inguinal lymph nodes were larger than pea-sized 11/12 (2nd day) The site of the injection slightly edematous and tender

3rd day The tenderness disappeared Place of the injection and neighbourhood discolored light yellowish green

5th day Glands unchanged *Discolorization of the skin indistinct*

6th day Inguinal glands enlarged On the right side two bean sized, on the left side one bean sized gland

9th day Inguinal glands protruding on the right side are smaller ones and almond sized, on the left side bean sized and some smaller ones In the region of the thighs and abdomen redness of the skin

10th day Light redness over almost the whole body, particularly on the parts where desquamation exists after scarlet fever Cheeks as if rouged The rash makes *at first sight the impression of a scarlet fever rash By closer observation* groups of very small to pea-sized hives are visible on different parts of the body Urine contains serum albumen Color of the urine is light yellow almost clear Sediment very scarce containing few hyaline casts

[illegible]

hives Many scratch effects Urine contains more albumen but still less than ½% Hyaline casts

13th day No rash, the eyelids slightly edematous

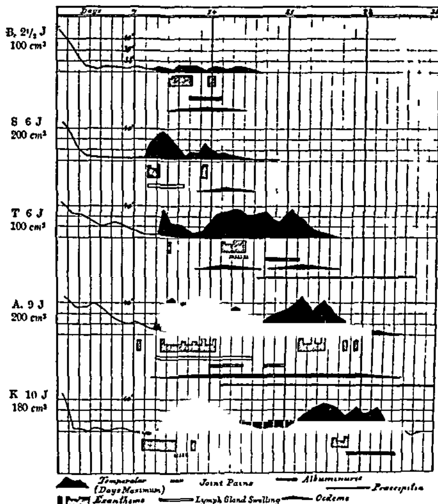


CHART III

14th day Temperature 39 1°-38 5° Small eruption of hives on the dorsal surface of the fore arm

15th day Yesterday afternoon fresh small sized, slightly elevated exanthema on the

16th day Temperature 38 2°–38 1°, loose cough On the thighs indistinct maculous erythema

18th day Vomited this morning On the dorsal surface of the legs brownish red maculous erythema The inguinal lymph nodes again larger than on the 16th day

19th day Temperature 38 9°–38.2° Erythema like yesterday Scrotum markedly edematous Coughing less Small amount of urine but no albumen No appetite

20th day Temperature 39 7°–37 9° Afternoon prostrated, much coughing Skin desquamating strongly on the abdomen and at the inner side of the extremities, sparcely on other parts of the body, spots of 1–2 mm diameter, brownish red slightly elevated, intensively pigmented, frequently confluent In the inguinal right region, two bean sized left greater than bean-sized lymph glands

21st day Pale remnants of the rash on the extremities

22nd day No rash

23rd day Temperature 39 0°–37 1° Medium-sized indistinct maculous rash on the thighs Inguinal glands right, almond-sized, left greater than bean-sized

24th day No fresh serum symptoms Pale remnants of the exanthema on the extremities Scrotal edema still present

26th day Temperature 39 0°–37 4° Indistinct medium-sized maculous exanthema on the thighs Inguinal lymph nodes as on the 23rd day

27th day Temperature 38 3°–37 3° No rash

28th day No fever, feels well

32nd day Inguinal lymph nodes smaller than beans Rapid improvement

37th day Inguinal lymph nodes much smaller, bigger than lentil-sized

On Chart IV the main symptoms of serum sickness, fever and rash, are shown connected with the daily determination of body weight and with the number of luekocytes We see at the top of the chart the weight curve During the first 9 days the weight is stationary With the onset of the serum sickness the body weight increases almost one kilogram in 4 days This rise is visible clinically as edema During this period of high temperature and breaking down of body protein loss of weight is expected, which is indicated approximately by the basic line of the weight curve The difference between the latter and the actual weight determined by the scale is taken as edema and marked by a shaded field. The edema is slowly excreted along with the diminution of the symptoms of serum sickness On the 23rd day after the injection the convalescence starts, recognizable by the now real increase of body weight representing new tissue The chart shows furthermore the leukocyte count taken daily in the morning at the same time on empty stomach The characteristic of the count lies in the intensive diminution in the number of leukocytes at the height of the disease The first drop takes place at the time of the eruption, another and more in-

the following manner The highest peaks of the daily temperature (the

temperature was taken 5 to 7 times daily) are connected. The rise in temperature due to serum sickness is shown as a black field.

Below on the chart the number of eruptions of rashes are marked as

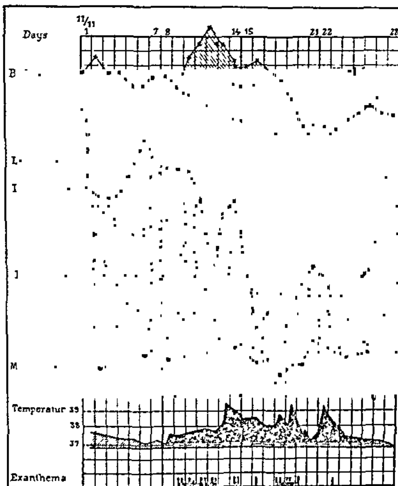


CHART IV

spikes. The basic line connects the eruptions, which with respect to their time of occurrence could not be separated distinctly enough

The amount of urine during the whole sickness was relatively small. The daily amount before and after the sickness was *500* to *700* cc., during the sickness 200 to 300 cc.

THE PERIOD OF INCUBATION

The serum sickness shares with many other diseases the peculiarity that the symptoms of the disease do not appear immediately after subcutaneous or intravenous introduction of the pathogenic agens Between the injection of the agens and the appearance of clinical symptoms, an incubation time exists In making this statement we disregard a little swelling, tenderness and redness at the site of the injection and the surrounding area which are the effect of the trauma caused by the injection (Chart V p 15)

The period of incubation cannot be explained by the slowness of the absorption of the foreign serum This serum exerts its antitoxic (diphtheria, scarlet fever) effect within a few hours When *Moser* injected scarlet fever serum he found it easy to follow the absorption of the serum because the scarlet fever serum agglutinates scarlet fever streptococci in high dilution From the determination of the amount of agglutinin in the serum of the injected individual, the beginning and the maximum of the absorption can be ascertained

Joseph R , 18 month old infant, was injected with 180 cc Moser serum, because it was a very severe case of scarlet fever Temp , 39 9° Afterwards, every 2 to 3 hours, blood was drawn from the ear lobe The serum part of this blood was tested microscopically for agglutinins in dilution from 1 4 up to 1 4000 against scarlet fever streptococci Whereas before injection no agglutinin could be found, already 2 hours later complete agglutination was present in dilution up to 1 16, incomplete up to 1 64 Now the content of agglutinins of the serum of the child rises rapidly and after 26 hours reaches complete agglutination up to 1 1000 From this height it drops slowly Parallel with the absorption the temperature falls as in a crisis As portrayed in the chart on page 15 the course of the temperature is reversed (drop shown as rise) in order to demonstrate the coincidence of the serum effect with the resorption of the serum

Symptoms of the serum sickness (hives and slight fever) appeared in this case on the 6th day after injection whereas the antitoxic effect reached its maximum after 12 hours and the resorption after 26 hours

Hartung has already observed that in more than half of his cases the serum symptoms did not appear until 10 days after injection Furthermore it did not escape his attention that serum sickness starts with preference on certain days which he called critical days *Daut* confirmed this observation Both authors would have found a greater uniformity and regularity in the length of the incubation period, if they had known the fact that persons who receive serum for the first time differ distinctly as far as the [illegible] from persons who have already

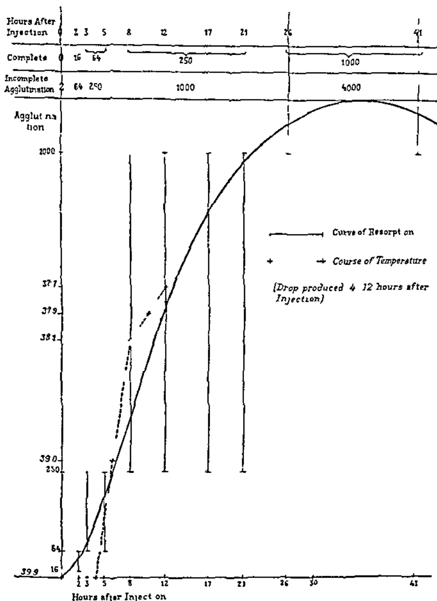


CHART V

strongly varying figures of other authors lies in the fact that the first symptoms of the sickness which can be taken as onset of the disease are at times local, at times generalized All according to what one considers as

CHART VI

the beginning of the disease, the duration of the incubation period varies 1 to 2 days We prefer to take, for statistical purposes, the general reaction of the organism as the end of the incubation period

In table 1 it is shown on which day after injection the serum sickness *started*

The upper section deals with the onset of symptoms in 90 children injected the first time, the lower with the onset in 45 reinjected cases The first heading contains the total number of cases, the second "questionable" cases in which it could not be ascertained whether they had received serum

TABLE 1

Days	1 and 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
							Onset on first injection									
Total	2	—	3	—	7	7	*16*	*16*	9	6	8	5	3	3	1	1
Questionable	1	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—
Local	—	—	—	—	4	3	3	—	—	—	—	—	—	—	—	—
							Onset on reinjection									
Total	*27*	—	1	3	*11*	2	—	1	—	—	—	—	—	—	—	—
Questionable	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—
Local	6	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—

before The third heading called "local' contains the cases which had only local symptoms (rash, edema at the site of the injection) It can be con

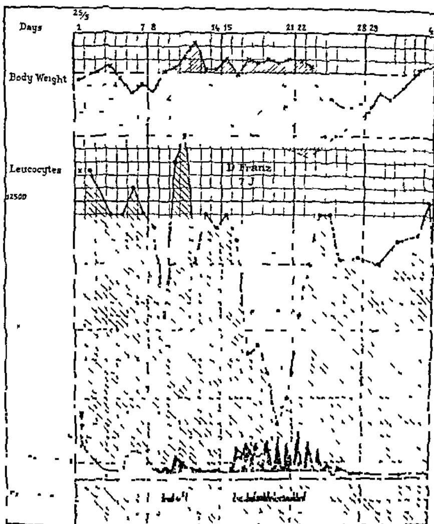


CHART VII

cluded from the figures in 90 cases of children injected the first time that the average incubation period is 8 to 12 days All statements made in this chapter deal with the first injection Reinjection will be discussed later in a separate chapter

From the table it can be seen that in the case of a first injection the

of symptoms occurs rarely before the 6th day Such a case we report on page 85 (Gustave P) The duration of the incubation period seems to depend for the most part upon the individual disposition of the injected child It does not depend upon the amount of serum injected

The variations in the length of the incubation time, which are conditional upon the different qualities of the injected serum, are relatively insignificant when one uses horse serum We did not observe that certain kinds of serum were combined with certain days of duration of the incubation time (*Hartung*) Whether the human being reacts to serum of animals other than the horse at different times were have too little experience to say

Netter (Soc med des hop , 1: 31, 1896) reports a child who showed, after an injection of 6 to 7 cc antipneumococcus serum of a rabbit, symptoms on the 12th day *Dallera* saw generalized urticaria 10 days after transfusion of lamb blood

Much less frequently than in acute infectious exanthema do slight disorders of the general well being occur during the incubation period As a rule it is completely free from symptoms The onset of symptoms of disease earlier than the 8th day shall be discussed later in the chapter on "Reinjection"

Fever

Since the days of *Wunderlich* there has been the endeavor to find a characteristic fever curve in diseases accompanied by fever Since then the course the temperature ran could be used for diagnostic purposes just as other symptoms of the disease With the varying intensity of all serum sickness symptoms we could not expect to establish a definite, unchangeable type of fever, only the following propositions can be made, particularly in regard to those cases, which received a greater amount of serum.

1 Fever is one of the most frequent symptoms of serum sickness It is more frequently observed than is the rash If one should want to name the disease according to the most typical symptom, one would be more correct to talk of "serum fever" than of "serum exanthema"

2 The fever lasts until the end of the clinical symptoms of serum sickness

3 The type of fever is a remittent one, the daily oscillations are 1 to 3 degrees It occurs less frequently that the temperature in the morning is also high Towards the end of the symptoms of serum sickness, when normal and subnormal temperature are often seen in the morning, an intermittent type develops

4 A certain connection exists between the temperature curve and the form of exanthema The highest temperature is seen in measles like (maculo-papulous) eruption, the lowest fever is observed with net like erythema, whereas urticaria and scarlatiniform rashes are in between

5 In general the height of the temperature does not permit one to judge the duration and intensity of the disease

6 The duration and intensity of the fever depend partly upon the amount of serum injected and partly upon the individual disposition

Comment 1 and 2 Our statement, that after an injection of a large amount of serum, fever is more frequent than a rash, refers only to the fact that at the height of the serum sickness the rash may be absent, whereas the fever continues

From Chart III we see clearly that fever occurs more constantly than the eruption of rashes

In case II (S) a period of fever lasting 3 days exists between the first and second eruption of rashes, in case III a 4 day period In the latter case no eruptions occur from the 16th day after injection although the fever lasts more than one week longer In case 4 we see fever existing throughout 8 days without a rash Still greater differences exist in case V

We lay great stress on the discussion of these facts in order to show that the term serum exanthema is not useful However we do not want to be misunderstood as far as the fever is concerned Enough cases exist where the fever is completely absent This loose relation between temperature and form of rash makes it clear that the fever is not to be considered as the effect of the exanthema *Fever and rash are coordinated effects of one cause* In favor of this sentence speak the facts mentioned in point 3

Comment 5 For the correctness of this statement the previous charts show examples

Franz D (see p 20) shows at the beginning of the sickness a low temperature for 3 days The physician who would have expected a mild and short duration of the disease would have been disappointed For on the 16th day fever started again, this time very intensive, lasting 10 days

High temperature of short duration is seen frequently after an injection of a small amount of serum (Diphtheria) The same observation can be made by an injection of a large amount of serum

Erna E , 150 cc scarlet fever serum Incubation period 10 to 11 days Slight increase of weight (edema 2) with high temperature The form of eruption is between

[illegible] on the whole disease is excellent

[illegible] pea in

9th–11th day Trousseau unchanged

12th day Temperature 37 6°–37° Since this morning disseminated over the body, indistinct, bright red, slightly elevated lentil-sized spots, in the left axilla a

packet of lymph nodes more than bean sized, in inguine both sides many small isolated lymph glands

13th day Today an intensive eruption of a serum rash Intensively red spots elevated up to lentil size densely located on the tensor surface of the extremities, frequently confluent, fresh papules standing singly surrounded by bright halos The eruption is between erythema multiforme, urticaria, and morbilli On the side of the neck just palpable lymph nodes, in the axilla packets like yesterday The inguinal lymph nodes are somewhat tender as yesterday Temp 39 3°–38 0° Mild itching General condition good

14th day The exanthema has progressed slightly Apparently the same eruption is present, it has progressed at the periphery The center of the spots is pigmented pale, greyish brown the periphery elevated and dusty red

15th day The same eruption present, it has progressed slowly down to the middle of the abdominal wall Beautiful multiform gyri on the lips The site of the injection does not show any reaction On the old field of eruption (tensor surface of the extremities) over brownish cyanotic ground a new eruption appears with bright halos Lymph glands in the left axilla unchanged tender Inguinal lymph nodes on the left side somewhat larger than on the right

16th day Temperature 39 0° 39 0° Slept well Exanthema spread to the left side of the abdomen, the rash on the extremities paler, pigmented Left eye sunken Conjunctiva both sides injected General condition good

17th day Temperature 39 9°–37 6° Yesterday afternoon a sudden new eruption of a rash covering the whole abdomen Today no fresh eruption, all over greyish brownish pigmentation In spite of high fever yesterday the patient felt well

19th day Temperature 38 0°–37 6° General condition good Discharged on the 32nd day, cured

Franz D Hospitalized 5/24–7/5/04 Lymph glands

Chart 7 p 17	Right	Left
Axillar	0	0
Inguinal	From palpable	to lentil sized

Spleen soft, 1 cm behind the costal margin

On 5/25 intensive scarlet fever (III) At 7 p m , 200 cc Serum 14, dated 2/12/04, was injected into the right side of the abdomen

2nd day Around the site of the injection distinct swelling

7th day Lymph glands not changed

8th day Inguinal lymph nodes over lentil sized

9th day Temperature 37 8°–37 2° On the region of the upper third of the right tibia some pale hives which itch intensively Inguinal lymph nodes the same

10th day This morning isolated eruptions of hives, at present indistinct

11th day Temperature 38 4°–37 2° Yesterday eruption of hives Face somewhat swollen Fresh, mostly large-sized urticaria on the skin of the right side of the body, particularly on the cheek and on the outer side of the right thigh On the left side only a few hives and they are smaller Inguinal lymph nodes the same, but they are hard and succulent Throat clean

15th day No fever no exanthema

[illegible]

mities, and the dorsum of the hand The maculae are isolated and elevated over the level of the skin Many inguinal lymph nodes are lentil sized and succulent

like design Feet On each side an

	right	left
Axillar glands	Small pea-sized	Pea-sized
Inguinal glands	Pea-sized	Below pea sized

The mucous membrane of the mouth pale Spleen enlarged, palpable at the costal margin

20th day Temperature 39 7°–38 4° Yesterday repeated eruptions of rashes Today a map like rash on the face, at the border a somewhat elevated, bright red, ring The center is pale, showing normal skin On the lower lip, about in the middle, a group of herpetic vesicles Patient feels well

21st day Temperature 39 6°–38 8° Also yesterday, all day, a rash Today pale remnants on the face which is edematous Maculo-papulous eruption on the lower extremities Herpes vesicles dried up Bad humor Inguinal lymph nodes pea sized

22nd day Temperature 39 7°–37 5° Yesterday again numerous morbillous eruptions, particularly on the calves Today the rash is pigmented with a cyanotic appearance,—besides this rash, isolated, fresh, morbillous eruptions On both forearms numerous, up to lentil sized, in the center paler, eruptions, definitely elevated, and at places, confluent Similar eruption on the thighs and in the left epigastric region Lymph nodes in inguine numerous, pea-sized, and succulent

23rd day Temperature 40 0°–37 2° Yesterday during the height of the fever, prostrated, at night quiet Yesterday's rash faded at the border of the old eruption On the fore arm and lower extremities fresh eruptions The eruptions show irregular borders The maculo-papulous spots have an elevated border are bright red, yellowish in the center, and sunken Throat clear

24th day Temperature 39 2° 37 4° Yesterday and today very few new eruptions

tled pigmentation on the extremities

27th day Temperature 38 6°–37 2° No rash any more

28th day Temperature 37 8°–36 8° Glands less swollen

29th day No fever

36th day Inguinal lymph nodes smaller than lentils

Now we report some cases which do not exactly correspond to the above mentioned relation between fever and certain eruptions Intensive urticaria eruptions without fever were reported by us before The following is a case where urticarial and morbillous eruptions showed the same intensity of fever

Henriette N 100 cc scarlet fever serum No 14 on 8/19/03 On the 6th day after the injection, following a lymph gland enlargement, fever and urticaria appeared which lasted five days Traces of albumen in the urine on the 9th 10th and 11th days after injection Then a lessening of the fever, of the lymph gland swelling disappearance of the albumen from the urine With a new rise of temperature lymph gland swelling and albuminuria Morbilli like rash with small sized maculi This eruption started twelve days after injection Nice weight curve, spleen is swollen

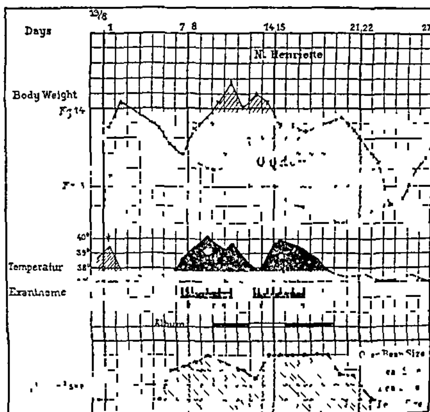


CHART VIII

The type of the temperature of the first symptoms of the serum sickness is that of a continua During the morbillous eruption, the intermittent character of the fever curve becomes distinctly evident The amount of urine was not substantially changed

Complete Case Report (Chart VIII)

Became sick on 8/17/03 with sore throat On 8/10 in the morning vomiting of mucus, then fever and scarlet fever rash Injection of 100 cc scarlet fever serum

During the first days some tenderness at the site of the injection but no other reaction

7th day Since yesterday afternoon urticaria on the abdomen, since the evening a generalized eruption of large hives with red halos, temperature 38 9°–37 6° Spleen not enlarged Lymph glands enlarged

8th day Continuing generalized eruptions of medium sized urticaria The skin is cyanotic, showing a design composed of small spots, at the buttocks net-like hemorrhages are visible, all over the body are scattered lentil sized hives with broad, red halos Many effects of scratching The inguinal lymph nodes protrude very much, forming on the left side almost a date-sized packet, on the right side about bean-sized glands, crural glands bean sized In each axilla a hazelnut-sized packet of enlarged glands, at the neck many glands over pea-sized, one gland at the maxillar angle is bean-sized Spleen hard and firm, palpable at the costal margin The mucous membrane of the mouth is pale Traces of albumen in the urine

sure At the lower extremities and on the face a scarlatiniform rash Lymph glands rather smaller Spleen palpable at the costal margin Feels well in spite of high fever Much scratching Traces of albumen in the urine

quiet than usual The eyeballs injected Trace of albumen in the urine

11th day Skin delicate, only indistinct remnants of the rash, temperature 39 6° At night restless, apparently joint pain, but the patient denies it with great stubborness Lymph glands definitely a little smaller Spleen at the costal margin On the posterior part of the skull more than pea sized lymph nodes Fine scaling on the face Less edema Weight decreasing

13th day Temperature 37 7°–37 3° Quiet, no rash Joint pain less Face only a little edematous Inguinal lymph nodes softer and smaller Throat clean and pale

14th day Yesterday afternoon a general eruption of a pale rosy red rash At night restless This morning a bright red, small, slightly elevated fresh eruption, [illegible]

bean sized In right axilla >1 up to bean-sized glands At each side of the thorax wall a lentil-sized gland At the neck many pea-sized glands At the occiput (right side) one pea sized, left, a lentil-sized gland Body weight decreasing Urine free of albumen

15th day Night quiet Temperature 39 6°–38 6° On the calves, on both forearms, a pale red, rather dense, small, not elevated eruption, some areas showing a ring formation Glands the same In the urine again traces of albumen

16th day Temperature 39 9°–37 7° Yesterday new eruptions The face in spite of loss in weight is more edematous All over fresh eruptions, loosely scattered Some confluence produces net-like designs Most dense is the eruption on the tensor surface of the upper extremities, on the calves between the scapulı The right occipital gland is tender Traces of albumen in the urine

17th day Temperature 39 8°–37 6° Quiet at night Yesterday during the day new eruptions, morbilli like in character, especially localized on the calves Today pale remnants of them are visible, some new eruptions scattered over the body Face distinctly edematous Trace of albumen

18th day Temperature 39 3°–37 8° Quiet, face less swollen On the side wall of the thorax and on the lower extremities pale remnants of rash The spleen can be reached behind the costal margin Trace of albumen

19th day Temperature 38 4°–37 2° No new rash Skin pale, dry edema unchanged Glands everywhere smaller and softer The two occipital glands hardly palpable anymore Pendulum rhythm of the heart

20th day Temperature 37 7°–37 3° Skin pale and dry Body weight decreasing Glands in inguine on the right side pea sized, on the left side nearly bean-sized, others pea-sized

23rd day Glands in inguine over pea sized not succulent any more

25th day Out of bed on 34th day discharged

Eduard G 4 years old 10/8–12/12/03 Medium severe scarlet fever, was injected with 100 cc Egmont" serum Inguinal lymph node palpable

8th day No fever Just now flat, skin colored hives appear Inguinal glands, left side just palpable on the right side bean sized

*9th day Temperature 37 4°–37 2° On different parts of the body lentil- and larger-*sized hives erupting without red halos Patient complains that he is bitten by fleas Left in inguine pea sized right one over bean sized and several pea sized glands In the right axilla a pea-sized gland

10th day Still more eruption of isolated hives without halo

11th day Yesterday the patient said, 'There are too many animals, I won't lie here anymore in bed" Continuous eruptions of urticaria, at the rounds pea sized and larger pale fine somewhat elevated hives, exclusively on the extremities *Inguinal glands on the right side somewhat larger than on the left No fever*

12th day No fever, feeling well Few pale hives on the outside of the extremities Here we see a case with intensive eruptions without fever

The following case runs a similar course

Olga L 3 years old 1/2–2/13/04 Injection of 200 cc scarlet fever serum No 4 (Fine), dated 10/7 on the right side of the abdomen injected on 1/2 midnight

9th day Temperature 37 5° 37 0° Skin pale only one hive on the skin of the back

10th day Glands not enlarged

11th day Yesterday afternoon at 5 o'clock an intensive, dense eruption of hives on the dorsum of the hands At 10 o'clock in the evening fresh urticaria eruption at the site of the injection and surrounding area not crossing the midline Today only one fresh hive on the dorsum of the right hand otherwise over the extensor surface of the upper extremities and on the dorsum of the hand irregularly formed red spots as well as scattered on the stem apparently fading hives

12th day Yesterday more eruptions of hives over the whole body, of which at present only pale irregularly formed remnants are visible No fever

13th day Distinct new hives on the right forearm and on the dorsum of the left hand Some *hives also over the inner malleolus of the right foot*

14th day No fever Yesterday some eruption of hives

Comment 3 The fever is remittent in character

In typical cases the fever almost never reaches its maximum in one day, usually the rise to the maximum develops gradually The fever drops showing a steep curve with a deep remission in the morning

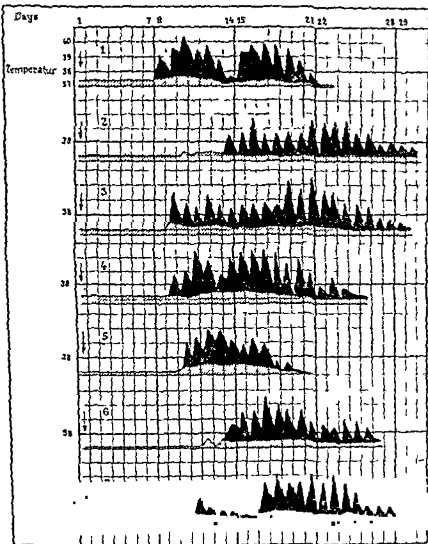


CHART IX

We report the following seven curves in Chart IX in which the fever is represented by a design different from the previous ones, in that we marked not only the maxima but also the minima of the day Curves 2 and 3 are

the fever chart of two injected siblings Note the similarity of the course of the fever

Other types of fever also occur, but they are much rarer No characteristic fever curve can be demonstrated for rudimentary forms of the disease

Through the gradual lytic drop in fever always showing a declining rise in the afternoon, the fever chart becomes as valuable a guide for the prognosis as the edema and lymph gland enlargement, which will be discussed later

Comment 6 Daut and *von Rittershain* established that the incidence of serum sickness falls with the amount of injected serum

In the first period of serum injections for the treatment of diphtheria when 10 to 30 cc of horse serum were used, symptoms of serum sickness developed in 22% of the cases *Von Rittershain* reported later a drop from this figure to 6 45% due to the fact that it had become customary to use a reduced amount of serum (6 to 15 cc) The best proof for the correctness of the statement that the incidence of serum sickness depends upon the amount of serum injected lies in the fact that, after an injection of 100 to 200 cc serum, we observed serum symptoms in 85% of the cases

We can conclude that the disposition for the disease is an universal one If we increase the amount of serum still further, finally every individual would develop serum sickness Whether an individual develops serum sickness after injection of a small amount of serum depends upon the disposition of the individual As it was to be expected, the intensity of the symptoms also becomes decidedly stronger with an increase in the amount of the serum Symptoms of such long duration as we have seen in cases which were injected with large doses never occurred after an injection of smaller amounts of serum (Chart III)

We may regard as proof of the influence of the individual disposition upon the course of the disease that sera, which otherwise only infrequently produce serum sickness, led to equal symptoms of serum sickness in siblings Siblings may show great uniformity even in certain anomalies of the course (as for instance, an abnormally short incubation period after a first injection), as siblings G reported on page 8 The following two cases give further proof of the similarity of the fever curve in siblings

Joseph W 2½ years, 10/24–12/8/03 Medium severe scarlet fever 10/24, 200 cc serum No III, dated 10/7, 03, injected at 10 00 p m Glands before injection

	right	left
Axillar	Peas	Peas
Inguinal	Small beans	

2nd day Site of injection painful
4th day Glands still unchanged
8th day The temperature rises again to 38 9°–37 9° Yesterday 8 cc diphtheria

serum was injected into the right upper arm At this site after 15 hours a local erysipelas like reaction

9th day On the stem a pale red small- and medium-sized, slightly elevated *exanthema*, dense on the abdomen, scarcer on the chest Left abdominal side shows more rash than the right Yesterday's erysipelas-like redness is paler today surrounded by 1 cm wide, intensively red, somewhat elevated halo, the latter again shows indented and island like extension Glands

	right	left
Axillar	Peas	Many under bean-sized
Inguinal	Several bean sized	One bean-sized

10th day On the stem and upper arm a rash consisting of yellowish-red, lentil-sized, slightly elevated maculae The areas of the previous rash on the abdomen and on the left flank show pale, confluent, redness and pigmentation, similar redness is seen at the site of the injection on the arm in a radius of about 8 cm At the periphery still a bright red zone with little infiltration Glands

	right	left
Axillar	Peas	Several under bean sized
Inguinal	2 over bean-sized	bean-sized
Crural	Under bean-sized	

Temperature 38 9°–36 8°, feeling well

11th day The whole body shows mottled pigmented remnants of the rash Spleen not palpable Lymph nodes

	right	left
Axillar	Under bean-sized	
Inguinal	Over bean-sized	Bean sized

12th day 38 9°–37 5° On the extremities bright red, frequently confluent, mottled, otherwise pigmented, faded, remnants on the right arm The side of the diphtheria serum injection and its neighborhood is like the site of the injection in the abdominal skin

13th day Temperature 38.8°–37 2° Fresh, bright red, slightly elevated rash, multiform with pale center, partly flat, partly showing lentil sized maculae Cheeks rosy, as if rouged red Glands

	right	left
Axillar	Many peas	Bean-sized
Inguinal	Many over bean-sized	Bean-sized

Spleen palpable at costal margin

14th day Skin on the thighs shows many creases Inguinal region desquamating, otherwise skin pale

15th day Since last evening a new eruption of rash, today pale to bright red, net-like design, on the back and tensor surface of the arms Lymph glands

	right	left
Axillar	Several below bean-sized	Bean-sized
Inguinal	Bean sized, almond-sized	Several bean-sized

Spleen not palpable

16th day Temperature 38 7°–37 2°. Yesterday afternoon and today fresh eruptions of bright red net-like erythema

17th day Continuous eruption of new rashes At the rounds, pale, net-like, design on many parts of the body Fresh eruption on the skin over the calves Skin very irritable

18th day Fresh net-like design on the back 38 4°–38 1° Glands as on the 15th day

19th day Temperature 40 1°–37 1° In spite of high temperature yesterday, lively and gay At night quiet On the back and tensor surface of the arms and legs, fresh multiform erythema Strong hemorrhages on places with pressure In the sacral region brownish purple palm-sized discoloration composed of confluent lentil-sized

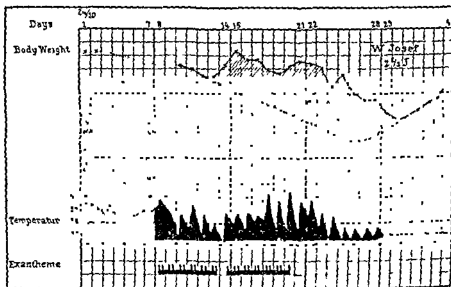


CHART X

maculi, which do not disappear upon pressure of a finger The skin on the inside of the thighs, wrinkled, scaling Bronchitis Lymph glands

	right and left
Axillar	Under bean-sized
Inguinal	Bean-sized

20th day Pigmented remnants of the rash of yesterday Fresh iris-like bands along the right outer margin of the foot No scratch effects Bad humor Frequent loose cough

21st day Indistinct remnants of the rash No fresh eruption 40 2°–37 5° Night very restless Mornings much loose coughing Lungs rough breath sounds In the evening one stool mixed with blood Microscopically mucus, red blood cells, very few white cells Serum reaction with horse serum, 1 1, no precipitation, with rabbit antihorse serum, distinct precipitation

22nd day Spleen at the costal margin Lymph glands

	right and left
Axillar	Many smaller than beans
Inguinal	Bean sized

Much loose coughing Breath sounds very rough particularly posteriorly Five soft stools with mucus, one almost entirely bloody

23rd day Glands

	right and left
Axillar	Many larger than peas
Inguinal	Bean sized

Since yesterday morning no stool and little coughing

24th day Temperature 38 9°–36 7° Stool normal less coughing and quiet at night

27th day Convalescent Patient in good spirits Little coughing Lymph nodes

	right	left
Axillar	Pea sized	Larger than peas
Inguinal	Bean sized	Bean sized

35th day Several times net like macular red spots appeared and disappeared rapidly

45th day Nodes

	right	left
Axillar	Many pea sized	
Inguinal	Two bean sized	Two smaller than beans

Adolf W 4 years old 10/28–12/8/03 Severe scarlet fever (No III) Inguinal lymph nodes on the right side larger than pea-sized On 10/29 at 3 p m 200 cc Scarlet fever serum (Egmont) Temperature fell 2 8°

2nd day Skin of the abdomen tender

3rd day On account of positive culture for Diphtheria bacilli 2 cc (600 A U) serum were injected Place of injection less tender glands unchanged

4th day Glands

	right	left
Axillar	Over pea sized	Pea-sized
Inguinal	Smaller than bean sized (60th)	

5th day Temperature 39 0° 38 0° Glands

	right	left
Axillar	Several bean sized	Pea-sized
Inguinal	Under bean sized	r>1

7th day Temperature 38 6°–38 1°

8th and 9th day Temperature 38 7°–37 1° Glands not changed

11th day Glands

	right	left
Axillar	*Over pea-sized*	*Almond-sized*
Inguinal	Over bean sized	Over bean sized

12th day Numerous pin point hemorrhages of the skin of diverse coloring scarce on the outside of calves and elbows very numerous ad nates and on the inner surface of the knees Otherwise the skin is pale

13th day No new hemorrhage

14th day Temperature 38 7°-37 4° Quiet, hemorrhage almost disappeared Glands

	right and left
Axillar	Under bean-sized
Inguinal	Bean-sized

15th day Temperature 38 7° Night restless Since this morning a pale red small sized, net like erythema eruption on the tensor surface of all extremities Stem free

16th day On the extremities pale brownish red pea-sized pigmentation, as after measles Axillar lymph nodes below bean size (both sides), inguinal glands bean sized

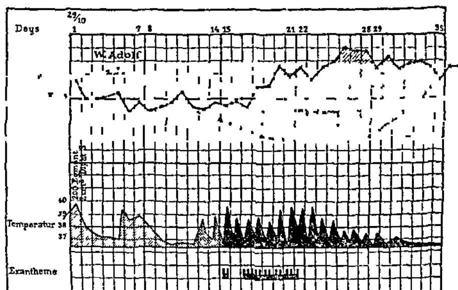


CHART XI

17th day During night in very bad humor, at the time of the rounds felt better Rosy red, multiform, exanthema on the outside of the extremities Otherwise rem nants of pigmentation stem still entirely free Axillar glands right less than bean-sized, left bean sized, tender, inguinal glands, right, more than bean sized left, bean-sized (Chart XI)

18th day Since previous night, erythema multiforma eruption on arms and legs, garland like, pale brownish areas Outside of these areas are pea sized, fresh red maculae Similar ones appeared on the abdomen, neck, and face Nose and forehead show confluent redness Eyelids slightly edematous Only the chest is free from a rash At the right angle of the mandibula, swellings that are tender 38.5°-37 7°

19th day Continuous new eruptions of erythema multiforme Lymph glands

	right and left
Axillar	Under pea sized
Inguinal	Bean-sized

Temperature 38 9°-37.3° During the night in a bad humor

20th day On the outside of the extremities, scattered pea- to bean sized, bright red eruptions with a pale, pigmented center

loose cough Lymph nodes

	right	left
Axillar	Pea-sized	
Inguinal	Bean sized	Below bean sized

At the rounds, pale brownish, slightly elevated pea- and bean sized maculae at the outside of the extremities

23rd day No new rash Temperature 39 4°–37 1° Before midnight very restless

24th day Temperature 39 6°–37 6° Night quiet Rapid respiration Indistinct pigmentation Lymph nodes

	right	left
Axillar	Palpable	Palpable
Inguinal	Under bean-sized	Bean-sized

26th day Rash disappeared Scrotum slightly edematous Appetite better Temperature 38 5°–37 4°

30th day Yesterday and today rapidly disappearing reddish net like exanthema on several parts of the body No fever, feels well

40th day Inguinal glands less than bean sized

As we have mentioned, 15% of the children treated with large doses of serum showed no clinical sign of a disease This low disposition of single individuals does however not mean a complete lack of sensitiveness

It is to be assumed with certainty that with these persons the same occurrences run their course (in principle) the intensity of the alteration however does not reach the threshold of clinical perceptibility

That the first injection alters the organism in a well defined manner, in spite of the absence of serum sickness, *can be concluded from the fact that individuals who* did not show any reaction after the first injection, behave when they are reinjected, in the same way as individuals who reacted the first time (see Chapter II)

The Exanthemata

This symptom which is so outstanding in serum sickness reveals itself in a great multiplicity of appearance The skin is inexhaustible in its production of peculiar pictures *Hartung* has already classified the rashes into four groups according to their appearance

1 Urticaria
2 Scarlet fever like exanthemata·
    a) Diffuse like an erythema
    b) Sprouting (really similar to scarlet fever)
3 Morbilli or rubella like eruptions
4 Polymorph exanthemata, among them exudative forms

Every observer will encounter cases which do not fit even in this many

groups We think that it would be better not to set every form of rash apart from the others because many cases show rashes which could be put, for example, either into the urticaria group or, on the other hand, also into the morbilli like group Transitional forms demonstrate that in reality no sharp line of demarcation exists as one would assume from the aspect of typical rashes As urticaria and morbilli like rashes are not so far apart we can still find even many more transitional forms between morbilli like or rubella like eruptions and exudative erythema multiforme We believe that the condition of the skin as organ determines the form of rashes more than the exciting cause In favor of this statement are observations in cases with numerous repeated and varying rashes

The first rash belongs in most of the cases to the group of urticaria Frequently new eruptions of urticaria appear for days at new areas, until the whole skin becomes involved After this form of eruption has terminated and a new eruption takes its place so it is the general rule that among such rashes no urticaria eruption is to be found The same can be seen when after a second eruption, a third and different rash appears To separate sharply the different forms of rashes would be justified only if we would make the rather unlikely assumption that in the serum different substances exist, each of them capable of eliciting different, specific rashes But then it would be necessary further to theorize that each of these substances must have a different incubation time, because almost without exception the morbillous rashes follow the urticaria, never the reverse

A further support of our opinion that the form of the rash essentially depends upon the condition of the skin, is given by the behavior of the eruptions after a reinjection We shall see that in cases of reinjection all symptoms therefore also the exanthemata, appear earlier than after the first injection, and also come to an end more rapidly If different substances were present in the serum, which could elicit different forms of exanthemata, then after reinjection we should observe different forms of rashes simultaneously, or one quickly after the other This almost never occurs As far as generalized rashes are concerned, they almost always belong only to the urticaria group

The observation of the course of rashes spreading over the skin of the body is made difficult because of the fleeting character of the eruption Urticaria eruptions are frequently preceded by redness, accompanied by itching and then only does a hive appear in the center of the red area

In one case we tried to follow exactly, hour by hour, how the eruption spread over the body, but we do not describe this case in detail, because even here we could not discover any definite law We wish to state only the following generalizations

1 Most frequently the rash first appears at the site of injection Some-

times this local rash is *the only symptom of the disease, as far as the skin* is concerned

2 The eruptions on the rest of the body are mostly symmetrical

3 The urticaria eruption is accompanied by intensive itching

4 The morbilli like and exudative eruptions are localized on the tensor surface of the extremities

We now describe some cases where many and intensive eruptions occurred In the case of Egon E (Chart XII page 34), we see urticaria of a four days duration, after a short intermission varied rashes appear, which according to their localization and appearance, must be called multiform The *onset and loss of edema is nicely shown on the curve of the body weight*

Egon E 10/8/03–12/6/03 At 7 p m 10/8 200 cc serum No 14 dated 9/18/03 injected into the right side of the abdomen In axilla and inguine several lymph glands *up to pea-sized right and left*

8th day Since yesterday evening eruption of urticaria At the rounds very large bright red areas in the center of which hives are visible (on the knees hands thighs) On the abdomen a rash which looks as if the scarlet fever rash had reappeared Inguinal lymph nodes at the right side several bean sized at the left side somewhat smaller Mucosa of the mouth pale Spleen not palpable

9th day Yesterday repeated eruptions of urticaria Today still partly macular like and confluent redness showing (particularly on the back) partly fresh urticaria eruption *in the region of the right shoulder and on the tensor surface of the right* knee joint intensive itching At night quiet Face decidedly edematous also the dorsum of the hand swollen by edema The hands are slightly cyanotic The lymph glands in the right inguinal region are succulent over bean sized apparently somewhat tender On both sides the glands are protruding Conjunctiva pale Throat clean Spleen can be reached Feet cold

[illegible] Edema one kilogram Continuously [illegible]

truding

11th day Temperature 40 2° 38 8° Very bad humor Skin on the stem dirty brown Extremities spotty as day before (fresh gyri) Lymph nodes more protruding

12th day Temperature 39 8° 38 0° Nose and upper lip slightly swollen and reddened On the lower part of the extremities fresh eruptions of erythema exsudativum multiforme On the gray livid skin lighter brick red irregularly defined areas the centers of which appear greyish blue Smaller red spots with indistinct colors are distributed over the body Nearby much pigmentation In the region of the [illegible]

On certain areas fresh multiforme exanthemata Throat pale Lymph nodes

	right	left
Axillar	Many less than bean-sized	Pea-sized
Inguinal	Sausage like protruding	Same

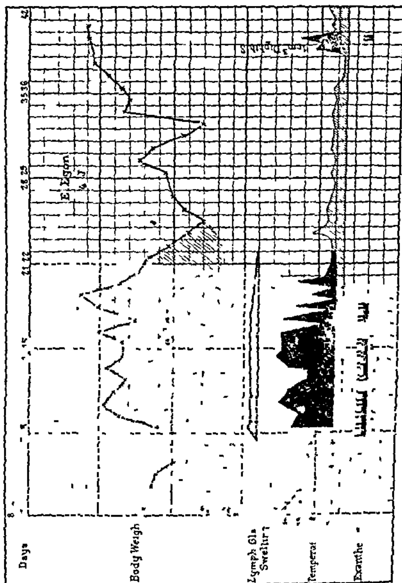

Days
Body Weigh
Lymph Gla Swellin
Temperat
Exanthe
E. Egon
21 22
28 29
35 36
42

Chart VII

14th day Temperature 40 0°–38 5° New universal eruption of erythema multiforme, particularly intensive on the extremities Patient is in very bad humor

15th day Temperature 40 1°–38 1° During night rather quiet Poor appetite Face, specially in the region of the eyelids, edematous, circa 1 20 kilograms of edema The face shows a rosy red, net like design, a similar design within the hair area of the skull On the arms, medium sized, macular, often confluent, erythema On the *thighs, similar eruption, on the calves and feet ring like eruptions* The ring appears to have an intensively purple color, which does not disappear upon pressure The center is livid, near by slightly elevated, brick red areas (*erythema multiforme*), the toes are livid Spleen not palpable, cubital glands not palpable In the right anterior axillar line in the height of the third intercostal space, two pea-sized lymph nodes Lymph nodes

	right	*left*
Axillar	3 to 4 hard, pea-sized	Same
Inguinal	Intensively protruding, hard, sausage like bean-sized	A little smaller

16th day Yesterday's small sized rash has entirely disappeared On the extremities brownish, livid, large design (pigmentation after erythema multiforme) Feet and dorsum of the hand, confluent, livid brown Glands like yesterday Temperature 40 5°–39 5° Quiet night

17th day Temperature 40 2°–37 6° Appetite better Loss of weight, ½ kilogram Stem and head free from rash On the extremities, near the livid remnants, fresh eruption of erythema Glands rather larger, spleen not palpable Yesterday in spite of high fever, temperature labile

18th day Temperature 40 1°–37 4° Condition again worse Yesterday four mushy, then *four brown bowel movements with mucus* In the evening sighing, but respiration not accelerated Very exhausted and tired On the extremities very widespread multiforme eruptions, the previous pigmentation has disappeared On the stem

remnants of the rash No new eruption In the urine questionable trace of albumen Sediment contains no renal elements

21st day Temperature 39 3°–37 6° No rash Feels well Swelling of the glands almost gone Lymph glands

	right	*left*
Axillar	Less than pea-sized	Same at the thorax
Inguinal	Bean-sized	Less than bean sized, not protruding any more

22nd day Axillar lymph nodes hardly palpable In inguine on the left side pea-sized, on the right side larger than peas Temperature 37.8°–37 4°

23rd day No fever (without aspirin) Edema excreted Tired Appetite better

27th day Temperature 37 6°–36.8° Axillar and inguinal lymph nodes pea-sized

31st day Glands the same Feels well

40th day Yesterday at 10 a m injection of 1 cc diphtheria serum, for immunization, in the right lower arm (Reinjection) In the evening, temperature 38 1°, arm

swollen At rounds the right arm is tightly swollen from the middle of the upper arm down to the fingers, the skin is diffusely red, hot, but not very tender Circumference of the lower arm is 18 cm (whereas the left arm measures 14 cm)

Glands in the *right axillar less than bean-sized*, left pea-sized

41st day Yesterday from noon to evening eruption of intensively red, about lentil sized maculae particularly on the chest, face, and external surface of the thighs Today at the rounds the skin looks normal, the right arm intensively swollen like yesterday, here the skin is pigmented brownish greenish (at the place of yesterday's diffuse red) Temperature 39 4°–37 4°

Axillar lymph nodes, right bean sized, left pea sized, inguinal glands left hardly palpable

42nd day Temperature, 37 7°–36 8° Still small swelling of the arm greenish

Otto D In this case a three-day urticaria period was followed by a two-day period of a morbillous eruption The duration of the sickness was short The edema was slight The swelling of the spleen and the behavior of the leukocytes was remarkable

Otto D 5/23–7/5/04 Scarlet fever of medium severity Inguinal lymph nodes, right, lentil sized left, pea sized 5/24 At 3 30 p m, 200 cc serum Vienna No 4 dated 2/12/04 injected into the right side of the abdomen

2nd day The side of the injection tender, the surrounding area of edema reaching the midline slightly edematous

3rd day The site of the injection less tender

4th day The site of the injection no longer swollen

7th day Glands unchanged

8th day Inguinal lymph nodes right larger than left Many nodes smaller than bean sized but not painful On right, one more than bean-sized, nearby pea-sized glands No definite rash

11th day Until this morning without fever A universal eruption of large penny-sized pale hives without red halo most intensively on the forehead, near the site of the serum injection and on the calves Intensive itching Glands like yesterday Whining disposition

12th day Temperature 38 3°–37 3° Yesterday during the day more eruptions of pale urticaria Today some fresh eruptions scattered over the body

13th day Temperature 38 0°–38 4° No rash

14th day Temperature 39 0°–37 8° The glands in inguine up to pea size

15th day Temperature 39 4°–37.8° Quiet Yesterday repeated eruptions of a morbillous rash on the cheeks and other parts of the body, mostly on the extremities Small spots are seen on the lower extremities, few on the stem, most numerous on the upper parts of the chest anteriorly Cheeks somewhat cyanotic, face intensively [illegible] edema on the [illegible] glands larger than pea-

16th day Temperature 38 7°–37 3° Yesterday no more rash, also today no rash, skin pale Face less edematous, no pain in the joints Conjunctivitis has receded Glands the same Spleen a little smaller and softer

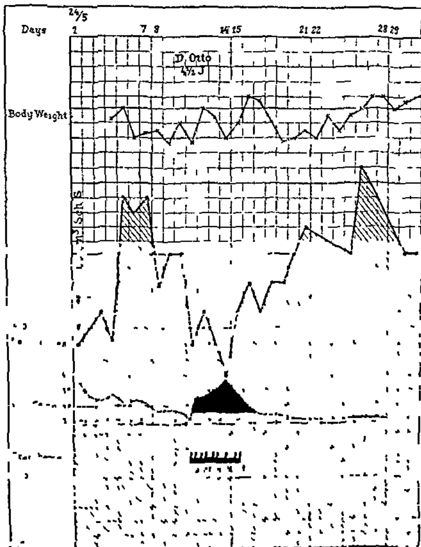


CHART XIII

17th day Temperature 38 0°–37 3° Face less edematous no rash
18th day Temperature 37 4°–37 2° Skin pale, inguinal glands pea-sized
24th day Spleen behind the costal margin
36th day Last evening at 6 30 p m 200 Antitoxin units (1 cc Diphtheria serum

was injected (Reinjection) After about 1½ hours a considerable swelling extending over the whole left arm Today this is still present The arm also shows a somewhat raised temperature

38th day Yesterday the swelling was less today only very indistinct

39th day Swelling has disappeared

Here we wish still to discuss separately two rare forms of eruptions The first group comprises the *cachectic form*, which is analogous to the cachectic forms of measles We find such eruptions in very debilitated patients The spots of the eruptions are then pale yellowish, washed out, particularly the hives which belong to the group are small, little elevated, the halo usually surrounding the hives is hardly present

Going through a long duration of intensive eruptions even the skin of a strong individual becomes pretty much exhausted, so that at the end of a long lasting serum sickness, the eruption may show a type similar to the just mentioned cachectic forms Especially we wish to call attention to a state of exhaustion of the skin which is occasionally found after injection of very large amounts of serum The skin appears edematous and irregu largly pigmented On the back are streaks of hemorrhagic suffusions produced by the pressure of the bedding By means of pressure, hemorrhages can be easily produced *Baginsky* talks about streaky hemorrhages

Another form of eruption is a hemorrhagic rash, which is very rare

Elly W Injected with 100 cc scarlet fever serum On the 11th day after injection a large eruption of urticaria appeared lasting 5 days Even at that time it was striking that after the urticaria there remained grey pigmentation surrounded by a fine red slightly elevated border On the 17th day eruptions started consisting of brownish distinctly elevated maculae of lentil size the center of which was dark blue At the same time there was high fever On the 18th day the described eruptions extended to areas 3 cm in diameter They were partly bluish red partly blackish, showing a narrow bright red demarcation at the margin The stem was free from rash down to the lower part of the back while the main eruption was found *on the* legs—less intensive on the arms On the face only a few similar maculae were visible The general condition was relatively good From the 19th day the eruption faded The black discolorization changed to a pale yellowish color Apparently the whole affair was rather a stasis of blood and not an extravasation

In this case we have to assume the existence of familiar disposition to severe rashes, because the sister of the patient also developed a very violent serum sickness after an injection of 200 cc scarlet fever serum, although without hemorrhagic exanthema

Very little is known about *pathological findings in the skin* during serum sickness As far as we know, no such investigation has been made on human beings, but only on animals, which also may develop rashes after an injection of foreign serum

Beclère, Chambon and *Ménard* injected calves with a large amount of

horse serum (1/100 of body weight) Four calves came down with generalized rashes and fever, one showed joint involvement Two calves injected with donkey serum showed no reaction The rashes were either like hives or like morbilli The cutis was intensively infiltrated Nothing characteristic was found by a histological examination *Aronson* saw not infrequently, a generalized eruption of papules after injecting horses with a foreign serum

Piorkowski injecting a horse with the blood of a syphilitic human being believed the ensuing rash to be a syphilitic eruption of papules We interpreted it in the manner of *Aronson* as the result of a foreign serum *Schuetz* examined the skin of this horse and found microscopically a small cell infiltration of the epidermis and subcutis combined with the disappearance of the corny layer The tissue slits were dilated

The Enlargement of the Lymph Glands

Hitherto enlargement of the lymph glands and edema were least considered as symptom of serum sickness

Finally *Adolf* and *Hartung* and later also *Freyberger* mention the occurrence of lymph gland swelling We attribute great significance to this symptom for two reasons (1) The swelling particularly of the regional lymph glands is one of the most constantly present symptoms of serum sickness (2) The swelling has great prognostic value Furthermore it is of general interest that the regional swelling informs us of which area of the skin the individual lymph node corresponds After an injection of serum subcutaneously into the skin of the abdomen in the first place the *lymph glands in inguine* of the same side become enlarged If there is a more intensive involvement of the lymph glands also the axillar glands and the glands in the fossa ovalis become enlarged From this we can conclude that the enlargement of the glands in this latter region does not always depend upon alterations in the genital region or in the lower extremities

The development of the lymph gland swelling after injections of larger amounts of serum subcutaneously into the skin of the abdomen takes its course in the following manner Seven to eight days after the injection a gradual increase in the size of the inguinal lymph nodes on the side of the injection is noted The previously palpable or lentil-sized inguinal glands become pea or bean-sized more succulent and protrude so as to become easily visible if one stretches the leg in the hip joint At the time of the onset of a generalized eruption a further rapid enlargement of the glands develops They often become the size of the pit of a date and larger and

then protrude like a sausage At this stage they are generally spontaneously tender and sensitive upon pressure During the first days of the general symptoms the swelling of the lymph nodes generally increases somewhat, also extends to other lymph gland territory and in certain cases increases to a *generalized adenopathy* As mentioned above, next the axillar and crural lymph nodes on the same side are involved, then these as well as the inguinal glands on the other side In some cases pea sized, succulent glands are felt at the side of the thorax and finally the glands at the neck and behind the ears become involved The enlargment of the lymph nodes continues until the disease is nearly ended, only the tenderness disappears earlier When the glands become smaller, softer and are less protruding we can infer that the end of the disease is near *The swelling of the glands precedes the onset of the disease and starts to recede before its termination* Herein, in this *behavior* of the lymph glands, lies its prognostic value Only exceptionally do new enlargements of the glands develop with a reoccur rence of symptoms of the disease

Franz K 13 years old 1/5–2/20/04 Scarlet fever, medium severe (III) 1/5, 3 00 p m , 200 cc scarlet fever serum No 8 dated 9/18/03

Glands before injection In axilla lentil-sized, in inguine up to pea-sized on the right side Spleen not palpable

2nd day The side of the injection painful, some edema extending towards the back

3rd day Glands the same During the next days nothing of importance The pain at the site of the injection disappears

8th day *Inguinal glands* protruding on the right side more than on the left, on the right side two glands together date pit sized and one bean-sized, on the left side several bean sized

9th day *Axillar glands* right bean and lentil-sized, on the left side pea sized In inguine as on 1/12

10th day Temperature 37 8°–37 0° Yesterday in the forenoon eruption of urticaria at first on the face, later spreading over the rest of the body Today almost nothing to be seen Mottled redness on the flexor surface of both fore arms *Spleen* distinctly palpable 1 cm before the costal margin Glands

	right and left
Axillar	Several over pea-sized
Inguinal	Distinctly protruding two about bean-sized and several under bean sized

Face somewhat edematous

11th day Temperature 37 4°–37 4° Yesterday new eruptions of hives In the [illegible]

14th day Temperature 37 9°–37 3° Yesterday pain in several joints Inguinal glands a little protruding, not so succulent anymore Crural lymph nodes, bean-sized, still protruding

15th day. The swelling of the lymph glands subsiding

16th day Inguinal lymph glands soft, not protruding, below bean sized Face slightly edematous No edema over the tibiae

17th day Temperature 38 0°–37 3° No rash Inguinal glands soft, they and the crural glands getting smaller Spleen somewhat smaller, palpable below the costal margin

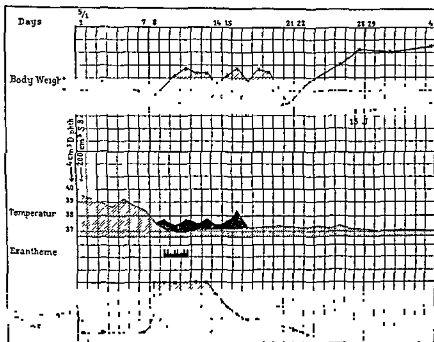


CHART XIV

19th day Spleen a little behind the costal margin Inguinal glands below bean-sized, soft

23rd day No fever Inguinal glands soft, rather long narrow In the right axilla lentil sized, glands on the left side palpable The glands at the side of the thorax not palpable anymore Feeling well

In this case the prognostic value of the swelling of the lymph glands is evident, because 24 hours before the eruption a rapid increase in their size was noted, as was a decrease before the end of the fever and edema, also here, as in the previous case, the acute enlargement of the spleen is found to run parallel with the swelling of the glands

Marie A 9 years old, 4/16-6/5/04 Scarlet fever medium severe (II) Inguinal glands palpable 4/16 at 10 00 p m 200 cc scarlet fever serum No 5 subcutaneously into the right side of the abdomen

2nd day Site of the injection somewhat swollen and tender (traumatic)

3rd day Site of the injection a little tender

4th day Site of the injection shows no reaction

8th day No fever Throat clean Right inguinal glands larger than left, shaped like a spindle and bean-sized

10th day No fever Yesterday afternoon eruption of *fresh hives* on the back also today some scattered on the back and around the site of the injection Cheeks mottled Mild itching The same glands not tender

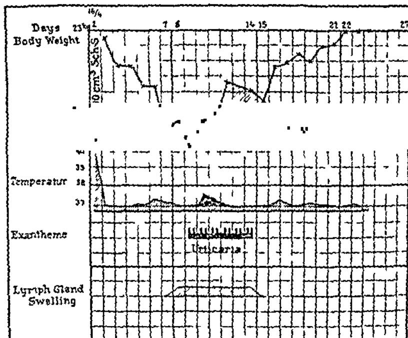


CHART XV

11th day Temperature 37 6° 37 4° Yesterday numerous hives on the face and extremities Today only a few fresh hives on the lower extremities

12th day Inguinal glands as on the 8th day No temperature Yesterday generalized urticaria eruption today fresh eruption mostly lentil sized hives on both knee *joints and their neighborhood* larger hives on the extensor surface of the tibia Large hives on the dorsum of both feet Intensive itching Throat pale

13th day *No fever* Yesterday hives on the face stem and thighs Today fresh hives over the tensor surface of both ankle joints and on the dorsum of the hands The skin of the latter region is thickened through accompanying edema, the fingers are swollen, the motility in the finger joints is restricted

21st day *No fever* Isolated hives on the lower extremities from the knee joints down

22nd day No fever, no rash Lymph gland swelling has decreased

The importance of the swelling of the lymph glands as a symptom of serum sickness is demonstrated by the following case

Heinrich S Scarlet fever of moderate intensity (II) On 3/6 at 6 00 p m 90 cc dried serum "Hoechst" At the time of admission several lymph nodes in inguine below bean size Injection on the right side On the 7th day the inguinal lymph nodes were still below bean size

8th day In inguine on the right side bean sized *protruding lymph glands* The other lymph nodes unchanged

12th day The glands in inguine a little more succulent The lymph glands in the fossa ovalis pea-sized right larger than left No rash

14th day Inguinal lymph nodes continue to be succulent, protruding a little over bean-sized

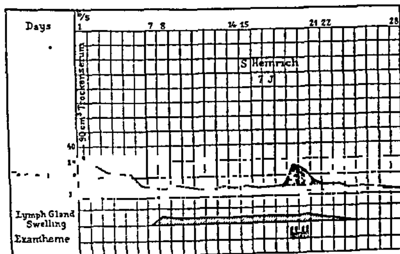


CHART XVI

17th day No fever glands the same No rash

19th day Tonight restless Itching In the morning universal *rash* composed of small maculo-papulous spots At the rounds this eruption was present on the back, particularly on the left side of the body and on the flexor surface of the upper extremities

1 1 – he

l

c

a

of a rash

21st day Skin pale

25th day Glands in inguine bean sized no longer succulent just a little prominent Feeling well

Inferring from the time of appearance of the rash in this case the serum sickness would not have started before the 18th day after injection We

see however that already from the 7th day after injection the lymph glands grew larger and remained bean sized for over a week, only then did eruptions of rashes and fever appear The swelling of the glands and other symptoms disappeared simultaneously This late onset of fever and rash is important for the problem of the incubation time Which day should be considered as the onset of the disease? Upon the beginning of the swelling of the lymph glands (7th day) or on the 18th day after injection when fever and rash appeared?

This difficulty in determining the beginning of the disease partly explains the varying statements of authors concerning the duration of the incubation time

Less frequent than the lymph gland swelling is a perceptible enlargement of the *spleen*, which lasts at most only a few days We refer to the cases *Franz K*, p 40, Ch XIV, and *Marie A*, p 42 Chs XIV and XVII

Finally the lymph gland swelling may also be the *only symptom of serum sickness*

Leopold F 10½ years, 5/17/04 Scarlet fever moderately severe (II) 4/10 injection of 200 cc scarlet fever serum No 6 dated 2/10 into the right side of the abdomen Site of injection somewhat tender at the beginning Inguinal glands a little tender upon admission, narrow, long, spindle-formed From the 5th day on there was a swelling of the lymph glands which continued growing larger until the 11th day The swelling declines from the 14th day No fever no exanthema

Gaston Poix found in his study of the pathology of lymph glands in serum sickness that, along with considerable enlargement, there were alterations in the parenchyma Findings in men have not been collected as far as we know *Czeczowiczka* (Zeitschr f Hlkde, 1903) treated rabbits with goat serum and examined the inner organs histologically

[illegible]

color was brought about by numerous granuli and scattered droplets, which were deposited into the cells (enlarged lymphocytes and swollen endothelial cells), filling them up very densely The granuli could be stained scarlet red orange red with sudan III But if osmium acid was used the results were irregular *Czeczowiczka* thinks that this substance belongs to the group of lipochromes

As for the rest no particular findings concerning the lymph glands could be recorded Sometimes the lymph sinuses were dilated Similar accumulation of lipochrome was found by the author besides fatty degeneration in the liver, particularly in preformed cavities of the intraacinous septa They may correspond to lymph spaces, whereas arteries, veins, bile ducts and liver blood capillaries have been free from such alteration In the

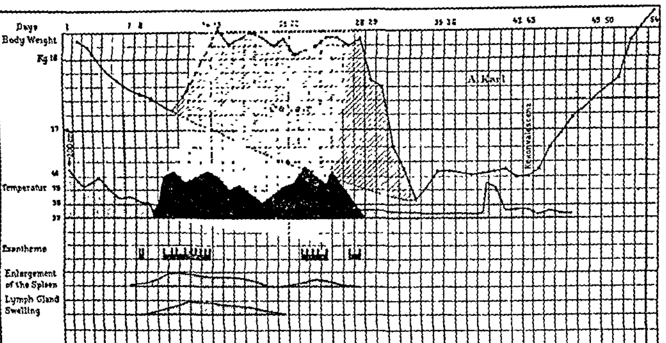

Days
Body Weight
Kg 18
17
16
Temperatur 39
38
37
Exantheme
Enlargement of the Spleen
Lymph Gland Swelling
A. Karl
Rekonvaleszenz

CHART XVII

spleen *Czeczowiczka* found much pigment and in the region of the Malpighi corpuscles accumulation of lipochrome, in the kidney fatty degeneration.

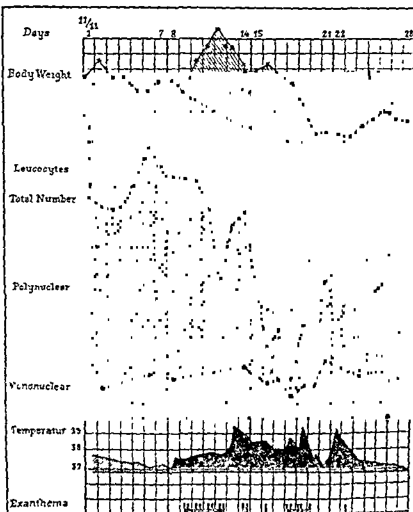


CHART XVIII

The bone marrow appeared rich in cells, frequently lymphoid, in the bone marrow cell many mitotic figures were seen

LEUKOPENIA

The importance of the leukocytes for the changes going on in a diseased organism makes it seem worth while to use at least the crude method of counting the number of leukocytes in serum sickness.

TABLE 2

Days after injection	Leukocytes among the Lymphocytes			Remarks
	Total number	Absolute number	In %	
day				
1	14,100	—	—	
2	13,980	2,100	15	
3	13,620	—	—	
4	14,000	—	—	
6	17,640	3,000	18	
7	16,120	—	—	
8	15,340	2,800	15	
9	15,480	—	—	
10	15,580	—	—	
11	13,620	—	—	
12	8,030!	—	—	First drop
13	12,500	—	—	
14	13,420	3,600	27	Mononuclear cells, strikingly many large mononuclear cells with broad protoplasma The nuclei *sometimes show* notches biscuit forms, here and there diffuse staining of the protoplasma (Tuerk solution)
16	4,620!	2,340	49 5	Leukopenia, relative lymphocytosis
17	5,500	2,820	54	*Relatively numerous* large *mononuclear* cells, about 0 9% Eosinophile cells scanty
18	2,530!	1,639	65	Lymphocytosis more pronounced Among them also larger forms with broad protoplasma which proves partly homogenous basophil The remaining cells mostly polynuclear forms with neutrophil granules Besides them mononuclear leukocytes with neutrophil granuli and transitional *forms* Eosinophiles very scanty
19	5,840	2,240	38 5	The increase in comparison to yesterday came about on basis of cells with neutrophile granuli In the dry slide is seen that the regular polynuclear cells are present in relatively small numbers There are relatively numerous leukocytes with large nuclei which look partly round, partly longish or kidney formed The protoplasma shows in the majority of cases, basophil, and occasionally, also neutrophile granuli

TABLE 2 (*Continued*)

Days after injection	Leukocytes among the Lymphocytes			Remarks
	Total number	Absolute number	In %	
day				
20	7,140	2,180	30 5	The true lymphocytes are rather in the minority Numerous large and transitional forms The number of polynuclear cells has risen since yesterday The increase of the total number is almost entirely due to them A further increase in the leukocyte count is expected for tomorrow because of the presence of many young cells
21	8,820	ca 4 400	50	Among them only 50% regular polynuclear cells All other cells are mononuclear and in a less degree lymphocytes Mostly large forms with a large round or longish nucleus
25	6 680	2,280	43	Only slight polynuclear leukopenia
27	8,120	3 020	37	Among the mononuclear cells lymphocytes are prevailing No large forms but still many transitional forms

The authors, who up to this time counted leukocytes after an injection of serum, limited this examination to the first days after injection, that is, to the first days of the incubation period This counting was done mostly for the purpose of studying how the number of leukocytes in a disease is influenced through the treatment with serum We however were particularly interested to study the leukocyte curve during the height of the serum reaction Therefore we made daily leukocyte counts throughout two to three weeks For carrying out this counting we wish to thank *Dr Eugene Fromm*

In some cases no worth while changes in the counts were found

Those cases, in which any really more significant alteration in the leukocyte count occurred, showed a very uniform behavior (Chart XVIII) *The leukocyte count rises moderately during the incubation period and suddenly falls considerably with the onset of the symptoms of serum sickness* The leukocyte curve reaches a low point from which the curve rises towards the end of the sickness to normal The course of the sickness in *Karl L*'s case has already been described in detail on page 10 Here we also consider the results of the leukocyte counts, which was carried out in this case by *Dr von Reuss*, to whom we express our thanks (table 2)

We observe therefore that the intensive drop in the number of leukocytes is

due almost exclusively to the reduction of the number of polynuclear cells The total number of luekocytes drops from 14,640 on the 7th day after injection to 891 on the 18th day The following increase of the total number takes place by the formation of new polynuclear cells, the reappearance of which is announced by young forms The mononuclear cells seem to be at first sight rather unchanged But upon closer examination we see that they are altered too With the onset of the relative lymphocytosis many large mononuclear cells appear with broad protoplasma as well as transitional forms, which disappear when the total number of leukocytes again rises

In one case we made the peculiar observation that the leukopenia was the only objective symptom of the serum sickness

Dr R Dehne Total number of the leukocytes after injection of 14 cc. antitetanus serum.

Before injection	8,500	
Day of injection	9,000	
2nd day	8 200	
3rd day	7,400	
4th day	5,000	
5th day	7,600	
7th day	8,200	
8th day	4,800	
9th day	5,200	
10th day	5,500	
11th day	5,400	
12th day	2,600	
13th day	2,500	Joint pain Towards evening feverish
14th day	3,300	Feeling sick
15th day	4,400	
16th day	11,000	Feeling all right
17th day	9,000	

Subjectively there existed simultaneously an intensive feeling of being sick, weak and exhuasted The case concerns a colleague who injected himself for experimental purposes with 14 cc tetanus antitoxin Therefore we can accept the subjective symptoms as correct This subjective symptom complex may occur especially with children more often than we can prove Whether or not the leukopenia may be the cause of the subjective symptoms we are not able to judge (Chart XX)

This behavior of the curve of the leukocytes reminds us very much of the leukopenia during the stage of eruption in *measles*, *smallpox* and *vaccination*

The chart on page 52 serves to illustrate this similarity, the figures of which we have taken from the fine study of *Sobotka*, dealing with vaccination

After reinjection we find the behavior of the leukocyte curve is altered (p 92)

The appearance of precipitin in the blood of the injected person and the connection between formation of precipitin and serum sickness will be discussed in the last part of our study (p 97)

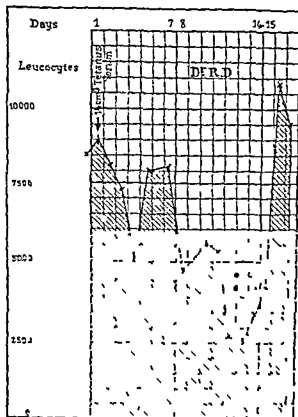


CHART XIX

JOINT SYMPTOMS

Hartung reports among 2073 cases of serum sickness, 140 cases of joint pains contributing 1 9% Among 4358 cases of a collective study on diphtheria serum, hardly 1% of the cases showed pain in the joints Therefore, joint involvement is not exactly a frequent symptom in serum sickness Likewise, "rheumatoid' pain in the muscles does not occur frequently Adults especially complain about the latter in the course of serum sickness

Hartung already pointed out that frequently the metacarpophalangeal joints are involved, second in line are hand and knee joints The involvement is characterized by intensive spontaneous attacks of pain increasing

by touch and movement The intensity of the pain is in striking disproportion to the entirely negative objective findings In some cases reported in the literature, exudate was found in the joint cavity, the joints felt hot, the patella was balloting We never observed such a case

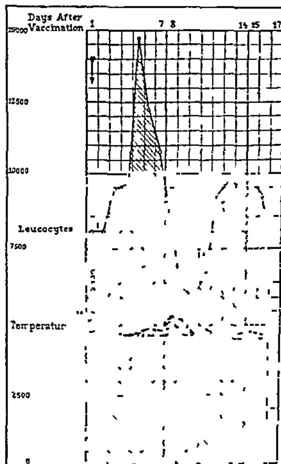


CHART XX

We must conclude just from the negative objective findings that pain and the whole *joint involvement* have a pathological and anatomical foundation different from acute rheumatism As the condition is benign no anatomic examinations exist in human beings *Beclère Chambon* and *Ménard* found in calves neither microscopic nor macroscopic changes, particularly no swelling, in spite of the fact that the joint pain was apparently very intensive

As the painfulness of the joints coincides with the eruption of rashes, so we suspected that perhaps similar pathology may develop on the synovial membrane of the joints as in the skin We never saw suppuration of a

Dr Lazar studied the course of the leukocyte count after injection of horse serum into rabbits He was so kind as to give us the results of his counts for publication

Data	Days After Injection	Rabbit 28 Leucocytes	Precipitin	Rabbit 18 Leucocytes	Precipitin	Rabbit 13 Leucocytes	Precipitin	Rabbit 20 Leucocytes	Precipitin
23 4	—	9,400		18,600		9,700		8,900	
25 4	—	9 800		10,200		9,100		13 200	
27 4	—	9,900		26,400		12 200		9 000	
29 4	2	10,400	0	23,000	0	12 000	0	13,400	0
1 5	4	10 000	0	19,600	0	11 800	0	*5,100*	0
3 5	6	*6,700*	0	*9,400*	Sp	*6,300*	0	5,000	+
4 5	7	5,400	—	9,100	—	7,400	—	5,200	
5 5	8	5,500	+	—	—	7,000	+	3,400	
6 5	9	7,900		14,200	+	7,500		6,400	
7 5	10	7,900		14,000		11,000		4 500	
8 5	11	—		9,000		—		3,600	
9 5	12	7,500		10,000		12,900		6 600	
11 5	14	7,800		11,900		8,000		4,800	
14 5	17	7 600		—		10,500		7,200	

Rabbits 28, 18, 13 and 20, had three counts of leukocytes taken in order to determine their average number before injection After that each of these rabbits received on 4/23/03 $\frac{1}{100}$ of their body weight of horse serum From then on about every day blood was withdrawn for counting the leukocytes and besides that the content of precipitin and of the precipitible substance was determined The last negative and the first positive result of examination for the presence of precipitin is recorded next to the figures of leukocytes

The drop in the number of leukocytes occurs in the rabbits earlier than in the human being in three rabbits on the 6th day, in one rabbit already on the 4th day Only rabbit 20 shows very low values (3,400), whereas rabbit 28, which gave the most *regular figures, dropped from 10 000 to 5 400*

The precipitin appears one to two days after the drop of the leukocyte count, a fact which indicates a connection between these two phenomena

joint, also never a disturbance of function afterwards and never complications involving endo- or pericardium

The painfulness of the joints makes the involvement of the joints one of the most unpleasant symptoms of serum sickness, particularly if several joints are involved The only consolation lies in the fact that the process is benign and that the symptoms disappear quickly Salicylates do not influence the process, one may safely forego their use Subjectively the most pleasant are cooling wet dressings with Burow's solution

The following case shows, in the second week after the injection, a series of eruptions of urticaria which were accompanied by edema but not with fever Then on the 15th day high fever set in, at the same time the joints became painful, the involvement of the joints spread rapidly over all joints, including even the joints of the jaw so that chewing was made difficult Only an indistinct erythema accompanied the period of the in volvement of the joints Furthermore, the spleen was swollen

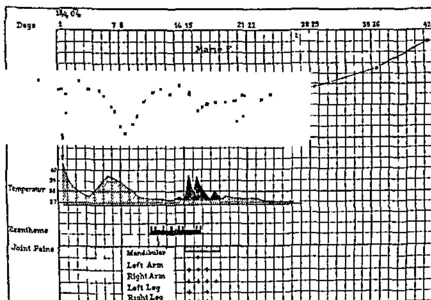


CHART XXI

Mary F 8 years, 4/18–5/29/04 Severe scarlet fever (III) 150 cc Scarlet fever serum No 5, Vienna, dated 2/12 was injected on 4/18 at 9 00 p m on the right side Inguinal lymph nodes on both sides bigger than millet grains Until 4/23 nothing noteworthy

hives the left,

but below lentil size

13th day Temperature 37 4° 37 3° New eruption of a few hives

14th day Isolated hives Today a fresh eruption of hives on the forehead Pale remnants of the rash on the lower extremities

15th day Glands the same No fever Some hives on the forehead and on the face only.

16 day Yesterday afternoon sudden onset of intense pain in joints of the *hands* and *feet* Sitting up was impossible Could not sleep at night Temperature at 7 00 p m , 39 2° Face distinctly edematous Cheeks spotty, reddened Conjunctiva in-

jected Pain on chewing in both jaw joints Today pain in the left hand and finger joints, *also in the joints of the left leg* No difference in the skin temperature between right and left No visible swelling Lymph glands in inguine right less than lentil sized left palpable both sides tender On the anterior side of the chest indistinct spots Spleen distinctly palpable a little below the costal margin hard Heart action excited heart sounds clear

17th day Temperature 39 3°–38 4° Yesterday urticaria on the face and intense pain *in different joints* *Today no rash* Pain only in the left arm The inguinal lymph nodes less tender

18th day 38 0°–37 1° No pain

19th day Temperature 38 0°37 2° Feeling well

20th day No fever

Edema and Albuminuria

According to custom we place these symptoms side by side without any intention of stating that we consider the edema as an effect of a kidney disease On the contrary, just in serum disease is it clear that edema and kidney symptoms represent coordinated symptoms Edema is, in the course of serum disease, an almost regular symptom, while albuminuria is only rarely observed

The localization of the edema is similar to nephritic edema It is seen above all on the face, only in the second place on the dependent parts of the body The edema is therefore certainly not an edema due to congestion The determination of the amount of edema is best carried out with a scale according to the idea of *v Pirquet*, who at first used this same method in nephritis The advantage of the method lies in the possibility that one can approach the determination of the absolute amount of edema Further more, small amounts of edema which could escape detection by the eye, can be determined objectively The weight is taken daily at the same time every morning

In order to evaluate the curve, which is composed of the separate daily weights, we make the well justified assumption that, in case of fever accom panied by loss of appetite a gradual loss of weight is to be expected If we see that in spite of these facts the weight increases, we ascribe this increase in weight, not to an increase in body substance, but to edema No conclusion can be drawn from only two successive figures of weight, but the total weight curve must be considered before passing judgment

The problem will be clarified by the following

might run, perhaps, a parallel course to the loss of weight during the first week of scarlet fever According to this assumption the body weight should have gone down to about 12 60 kg Instead of that the body weight rises from 13 40 kg to 14 40 kg At the same time we find in the record of the case the note that the face, particularly the eyelids, looked very edematous for many days We now take this difference between the supposed and the actual weight curve as edema, and get in this way at least an approximate idea of its amount In this case it amounted to about 1 80 kg

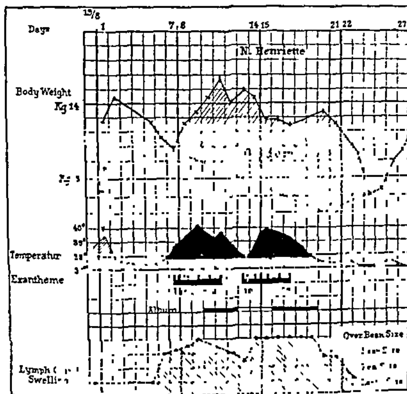


CHART XXII

With the retrogression of the serum symptoms, the body weight falls more or less rapidly to its true level The edema was excreted and was not visible anymore After having reached the lowest point the weight curve again rises This rise is due to a real increase of body substance (see Karl A, chart on page 46)

The duration of the edema corresponds to the duration of the disease *The decrease of the edema has a prognostic value similar to the diminution of the lymph gland swelling*

If *albuminuria* appears at all as a sign of irritation of the kidneys,

it does not set in until several days after the onset of the edema These authors, who until now occupied themselves with the much disputed problem of albuminuria after serum injection, looked for the albumen immediately after the injection or during the days following the injection of serum But albumen is found only at the height of the serum sickness, in the second or third week after injection In our cases the amount of albumen was never higher than ¼ pro mille In the sediment free red cells and hyaline casts are found The amount of blood is always so small that it can not be detected macroscopically

We never saw hemorrhagic nephritis due to serum as has been described by *Freymann*, *Guinon* and *Rouffillage* We are, in this respect, in agreement with all other authors Taking into consideration that serum therapy was chiefly used against diphtheria and, by us, also against scarlet fever, we must be particularly careful in judging albuminuria and edema, because both these diseases may themselves lead to serious kidney involvement The clinical observation of the symptoms can supply sufficient differential diagnostic clues, which permit us to separate them from the symptoms of diphtheria and scarlet fever Diphtheria shows no edema even with severe kidney damage Edema develops only on account of weakness of the heart, and then it presents the character of edema due to congestion (*von Pirquet*) The symptoms of an irritation of the kidneys in diphtheria start almost always during the *first days* of the disease, show only a slight formation of sediment and a small amount of blood, but often show a substantially higher amount of albumen Besides, the distinction between albuminuria in serum sickness from the diphtheric form has little practical importance, because, in consequence of the small amount of serum used in the treatment of diphtheria, albuminuria due to serum hardly ever occurs

The situation is different if we inject large amounts of serum as we are accustomed to do in scarlet fever Here the question more often arises whether the edema and urine findings are due to serum sickness or scarlet fever Edema with negative urine findings at the height of the serum sickness one can almost certainly relate to the serum The simple edema of scarlet fever described by Quinke in some cachectic children is certainly very uncommon We did not see any such case among 500 cases of scarlet fever observed during the last two years where we carried out exact determinations of body weight Furthermore, the edema due to serum starts about one week earlier than the edema of scarlet fever nephritis In the rare cases where we find edema together with urine symptoms, the differential diagnosis is facilitated by the time when the sediment appears Large amounts of albumen and blood, a mass of sediment, indicate with certainty the presence of scarlet fever nephritis Likewise, uremic symptoms and intensive edema prove the scarlet fever character of the process

in question, as edema due to serum keeps within moderate limits, uremic symptoms never develop We never saw an accumulation of edema fluid in the pleura or in the peritoneum No hypertrophy of the left ventricle occurs, the blood pressure is not materially influenced

We have seen some cases where, in the couse of the serum sickness and the accompanying edema and albuminuria, a true scarlet fever nephritis developed In the following case it can be shown that the onset of the nephritis is sometimes well marked (Chart XXIII)

The serum sickness starts with a rise in body weight on the 10th day [illegible]

with the naked eye The edema disappeared with the fall of temperature Suddenly on the 17th day of the scarlet fever albumen is found in the urine in large amount (more than 1 pro mille) Two days later the curve of the body weight rises sharply, so that after the elapse of one week it surpasses the minimum weight of the patient by almost three kilograms From this point on the body weight and the albumen in the urine decreases gradually

Heinrich S 10 years old, 1/4–3/13/04 Medium severe scarlet fever Moderate throat symptoms Injection of 200 cc scarlet fever serum No 12 on the 4th of January at 11 00 p m into the right side of the abdomen Glands

	right	left
Axillar		Below lentil-sized
Inguinal	Pea sized	Below bean

2nd day The region of the injection and its neighborhood swollen, very tender Towards the back and upward a half spherical swelling the size of a baby's head (poor resorption)

3rd day Temperature 40 2°–38 2° The scarlet fever rash increased during the day and is still today vivid red and small, visible on the back Other places show an indistinct rash During the night restless, hallucinating Today fresh Throat less swollen No exudate on the tonsils The site of the injection less swollen but tender Spleen palpable

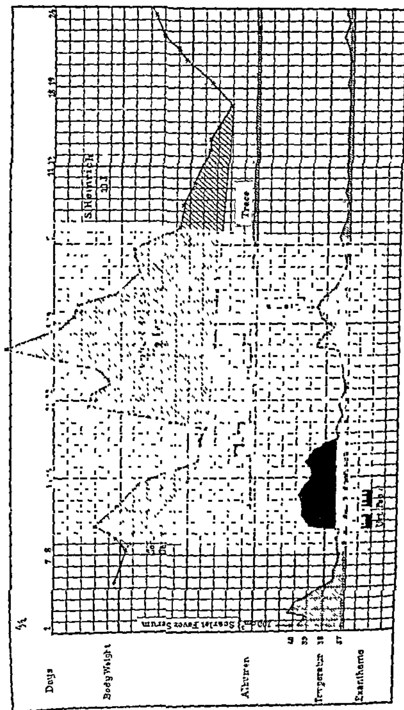
4th day Temperature 39 0°–38 0° Night restless this morning much fresher Rash has faded, fine desquamation is starting Glands the same Throat paler, less swollen so that the space in the pharynx is twice as large compared with the width on admission Spleen palpable below the costal margin

5th day Temperature 38 2° 37 2° Fine desquamation, remnants of the rash

6th day Inguinal lymph nodes below pea size and longish

8th day Skin pale, no fever

9th day Intensive desquamation on the inside of the left upper arm on the right [illegible] dense eruption of bright red, somewhat [illegible] both upper arms [illegible] ition of medium to large vivid red, distinctly elevated maculae on the left side confluent to large



Days
Body Weight
Albumen
Temperature
Exanthema
40
39
38
37
200 cc Scarlet Fever Serum
S. Heinrich
Trace

CHART XXIII

areas On the lower part of the back less red and more isolated maculae Lymph nodes

	right	left
Axillar	Over pea-sized	Bean sized
Inguinal	Many below bean-sized	

11th day Temperature 39 0°–38 0° Yesterday afternoon an eruption of small, loosely arranged, vividly red, somewhat elevated maculae on the stem Densely arranged, up to lentil sized maculo-papular eruption appeared on the calves and dorsum of the feet The eruption is today still very distinct and vividly red Isolated maculae also on the thighs and tensor surface of the upper arm The maculae described yesterday flatter and paler *Face* free from rash, *slightly edematous*

12th day Temperature 39 4°–38 6° Body weight increased 450 grams Face *distinctly puffy* *Edema of the dorsum of the hand* Yesterday's maculae paler, however there are fresh eruptions (maculae) in the face Densely arranged more papular rash on the extensor surface and inner surface of the calves and the dorsum of the feet and also on the extensor surface of the arms from the middle of the upper arm down to the lower end of the forearm On many areas the rash has the appearance of an erythema exudativum multiforme, which is brought about by the paleness of the central part of the eruption Lymph nodes

	right	left
Axillar	Several more than pea sized	Hazelnut-sized
Inguinal	Both sides bean-sized, protruding not tender	

13th day Temperature 39 4°–39 2° Somewhat exhausted, no special subjective complaint, little sleep at night Yesterday new eruption of maculae which are today paler Fresh eruption of maculae on the dorsum of the hands and extensor surface of the forearm to the middle, as well as on the extensor surface of the fingers The rash is maculo-papular, in size from pin head to larger than lentils Many maculae, in the center, paler and flatter Similar eruption of a few spots on the skin over the patella Face looks puffed Glands the same Loss of weight

14th day Temperature 39 7°–39 0° Yesterday and today more exhausted than usual Night restless Pain in the left side Yesterday new eruptions This morning no fresh spots Generalized desquamation Lymph glands

	right	left
Axillar	Pea sized	0
Inguinal	Several bean-sized	Slim, larger than beans

Glands everywhere less succulent and do not protrude so much in inguine

15th day Temperature 39 0°–38 5° Night sleepless, today in the morning still tired Body weight went down no rash Face less puffy The inguinal lymph nodes softer, *smaller*, hardly protruding any more

16th day In bad humor During the night pain in the abdomen No rash Desquamation less, face less puffy The body weight is going down The abdomen all over tender by pressure

17th day Temperature 39 1°–38 4° A little quieter, complains still of abdominal pain, no rash Mucous membranes anemic Inguinal glands no longer protruding On the right side one gland less than bean-sized otherwise on both sides longish, small glands, not tender

18th day Temperature 38 8–°37 6° Towards evening abdominal pain again Skin

pale, no rash Face only slightly puffy Inguinal glands larger than peas soft Spleen 1 cm behind the costal margin

19th day Temperature 37 4°-37 0° Face pale, almost no puffiness

20th day Temperature 37 5°-37 0° No rash, appetite better

21st day No fever Inguinal lymph glands larger than pea sized

23rd day Heart action a little arhythmic

24th day Until yesterday the urine contained traces of albumen Today urine 550 cc *reddish, much sediment* Patient is decidedly more exhausted No visible edema Body weight increasing Heart action arhythmic, slow Heart sounds are clear

25th day Amount of urine, 500 cc *Body weight increased 550 grams* Urine cloudy, shows a great deal of bloody sediment The sediment contains red blood cells, nu

27th day Yesterday small macular eruption on the face Today only pale red remnants visible on the left side Vividly red maculae on the extensor surface of both arms, also on the lower extremities Glands the same

28th day Temperature 38 5° 38 4° Yesterday afternoon a *mottled redness over the whole body* Today skin pale

29th day Temperature 37 6°-38 2° No subjective complaints Face distinctly puffy Also on other areas of the skin finger impressions persist Urine 350 cc (specific gravity 1017) Dark reddish brown sediment Heart dullness not enlarged Heart sounds somewhat like murmur

30th day Temperature 37 6°-37 5° Night very restless Complains about ab dominal pain Nose bleeding, today very tired, nausea Very little food intake Urine 450 cc (specific gravity 1015)

31st day Yesterday during the day tired, afternoon staring look sometimes con fused Pulse not particularly tense Vomited once At 8 30 p m *onset of uremic con vulsions*, loss of consciousness The convulsions are mostly in the right half of the body Uncoordinated movement of the eye balls The convulsions are tonic-clonic Pupils were wide, not reacting to light Pulse 150, tense All vessels visibly pulsating Immediately after the onset of the convulsions a venesection is performed on the

reddish yellow Patient is still quite exhausted Sensorium free Heart dullness somewhat enlarged to the left Apex beat in the 5th intercostal space in the mammillar line Heart sounds clear

32nd day Temperature 38 0°-37 4° During the day happy, nights quiet *Loss of body weight* Urine 300 cc, contains less blood

34th day No fever

35th day Profuse diuresis

37th day Face pale plenty of urine which contains a trace of albumen

46th day Heart enlargement disappeared convalescent

It is easily understood that we tried to develop an idea as to what im portance the edema plays in the course of serum sickness We are of the opinion that the edema is a primary symptom of the disease and not the

expression of a secondary damage It is analogous to the rash and the lymph gland swelling The edema is not due to congestion or insufficiency of the kidney Our conception is corroborated by the close relation between urticaria and edema This we see most clearly in the eruption of urticaria in the face

Garnier and *Sabaréanu* found that at the time of the purulent dissolution of the smallpox eruption the body weight rises These two authors are of the opinion that this increase of body weight is due to a localized inflammatory edema which belongs to the course of the reaction, and that it is necessary for the healing process We consider that the edema in serum sickness is in similar way a symptom accompanying the pathology created in the skin

Behavior of the Mucous Membranes

[illegible] ness [illegible] e of [illegible] hing serum sickness from scarlet fever and measles Contrary to the findings of *Hartung*, we have never seen a case of tonsillitis due to serum in spite of our attentive observation

Mya reported that children who were injected with diphtheria serum against croup again showed symptoms of stenosis of the larynx during serum sickness The cause of which is the development of a subglottic edema He explains the connection with the assumption that the mucous membrane, damaged by the diphtheria process, is predisposed to the development of swellings

We report one case of subglottic edema that came under our observation

[illegible] and had to be imme [illegible] /13 on [illegible] s per [illegible] child complained about pain in the fingertips and toes soon afterwards [illegible] viv- [illegible] appeared on the legs Temperature rose to 37 9° [illegible]

However it was not seldom that we found simultaneously with other serum symptoms, signs of a *diffuse bronchitis*, and in some cases *bloody diarrhea* develops lasting several days As *Hartung* has already remarked, the causal connection between bronchitis and serum sickness cannot be

proven, however such a connection between bloody diarrhea and serum sickness seems to us very likely We could never relate with certainty rhinitis and conjunctivitis with serum sickness However we have twice observed, simultaneously with skin eruption, lentil seized red elevation in the conjunctiva of the bulbus See *Josef W*, p 33 On 21st day, Egon E, p 26 on 18th day

The General State of Health

We have mentioned before, that in mild cases of serum sickness the general state of health is remarkably little affected The good general state of health is frequently in contrast to the high temperature Restlessness, whining disposition, easy irritability occur very frequently, *Cnyrim* reports in his case symptoms of neurasthenia Vomiting is very rare Only if the sickness lasts very long does the patient become very tired, loses appetite and in the severest cases may become considerably prostrated In connection with the small intake of food such patient become emaciated, which is particularly noticeable after the disappearance of the edema This loss of weight is analogous to the loss of body weight in experimental animals after repeated serum injections But even in extremely severe cases no danger to life exists The severest case of serum sickness we observed is the following

Chart XXIV, Max P

Here we see fever periods in the 2nd, 4th, 5th and 7th week after *injection which resemble* each other Sudden onset, and rise of temperature remittent in type followed by lysis Exanthemata and generalized lymph gland swelling are present during the first and second periods Traces of albumen accompany the second to fourth period Edema was observed throughout the whole course of the periods *At the onset of fever increased retention* of fluid occurred The greatest intensity of edema was seen simultaneously with the fourth period of fever From then on the edema was excreted but not until the tenth week did it yield to a real gain in body substance representing reconvalescence In the sense of medical history we must count this clinical picture of a nine week duration as a chronic disease ending in recovery Thus we see that we have before us a chronic disease produced by a single injection of a substance which can not multiply The peculiarity in this case is that one injection can produce a repetition of four similar periods of symptoms of a disease separated from each other The principle importance of this observation is not reduced by the exceptional rarity of such cases, we do not lay any particular value on term "chronic" because we have seen all transitions from this case to a case of short duration

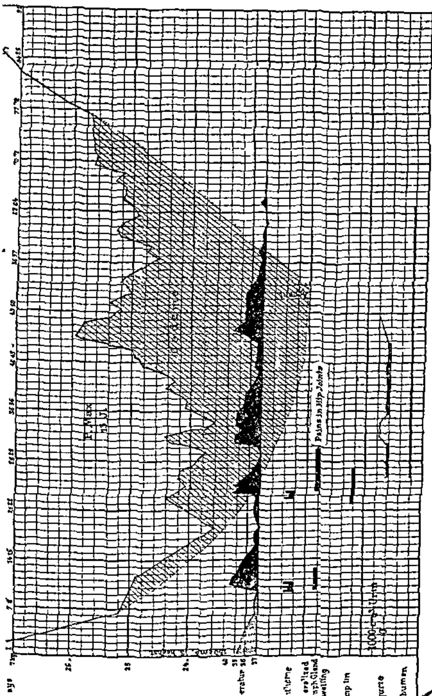


CHART XXIV

Differential Diagnosis

The similarity of the rashes during the serum sickness to the rashes in scarlet fever, measles and to toxic rashes often makes the consideration of differential diagnosis necessary Furthermore we often have to decide the question, whether isolated symptoms such as fever, albumen, edema are due to the serum Injections almost always involve sick individuals except in cases of immunization and the primary disease is not entirely eliminated by specific treatment In the first place we should not make the mistake of assuming that in every case of unexplained fever at the time of serum symptoms this fever is to be ascribed to serum

From the viewpoint of differential diagnosis, scarlet fever and measles are the most important diseases Relative to this *Baginsky*, *Monti* and *Hartung* have already called attention to important characteristic distinctions Of importance we consider the following symptoms which favor the diagnosis of serum sickness

1 *The time of the appearance of the rash (7–14 days after injection)*
2 *The first eruption at the site of injection*
3 *Regional lymph gland swelling*
4 *Complete absence of symptoms on the mucous membrane*

Point 4 makes it easy to distinguish measles from serum sickness the absence of Koplik spots, coryza, and conjunctivitis constitute sufficient differential features To distinguish *serum sickness from scarlet fever* is most difficult, it is sometimes impossible In many cases only the spread of the disease to other children, the appearance of characteristic desquamation or the onset of hemorrhagic nephritis clarifies the situation, showing that the supposed scarlatiniform rash was true scarlet fever *Leiner* reported such a case Influenced by this some authors questioned the existence altogether of a scarlatiniform rash in serum sickness We have seen cases showing a scarlatiniform rash, where we could state with certainty that it belonged to serum sickness On the one hand children who were treated with serum on account of scarlet fever developed in the course of serum symptoms a scarlatiniform rash without any other sign of a relapse of scarlet fever, on the other hand we observed the following two *children developed* a scarlatiniform rash after an injection of diphtheria serum and were for that reason transferred to the scarlet fever ward After a few days they developed a typical scarlet fever

As distinguishing features of scarlet fever in contrast to *the scarlatiniform* rash in serum sickness we can cite the following

1 Vomiting at the onset

2 The existence of a sore throat and inflammatory redness (Enanthema) of the mucous membrane of the mouth at the same time as the rash

3 Very high temperature

4 In a hospital the outbreak of scarlatiniform rashes at the same time or in short intervals The value of point 4 lies in the fact that scarlatiniform rashes are rare in serum sickness

The distinction of toxic (mostly drug) rashes from serum sickness would often be very difficult, in reality there is rarely an occasion to make such a decision The symptoms of serum sickness do not develop until several days after injection At that time the patient is treated for his primary disease If a drug would be administered which according to experience may at times produce rashes, a repeated administration of the drug will clarify the problem Urticaria caused by alimentary disturbance has to be more frequently considered Location of hives at the site of the injection and swelling of regional lymph glands indicate serum as the cause, gastro-intestinal symptoms, alimentary urticaria

Therapy and Prophylaxis

The symptoms of serum sickness do not respond to etiological therapy After the foreign serum is once inside the organism, the latter is forced to go through the reactions induced by the foreign substance in order to get rid of it To interfere with the course of these reactions would be useless if not harmful If one likes to discuss therapy at all, it could only be a symptomatic therapy We apply Burow's solution on the area of the injection, if this region is tender and swollen, and on the extremities warm, local baths of long duration, which are found to be very pleasant The itching, which mainly accompanies eruptions of urticaria can be mitigated in some measure by rubbing the skin with 1 to 2% salicyl alcohol or 1% menthol [illegible]

and profuse sweating, but the effect is of very short duration As we have already mentioned, the salicylate has no influence upon the joint pains We recommend local warm packs and baths For diarrhoeic conditions, the customary styptic drugs with dietetic measures may be tried Edema and albuminuria do not allow themselves to be combatted

Finally it remains for us to discuss the effort to avoid serum sickness by the removal of the etiological factor As the antitoxin as such has nothing to do with the damaging complications of serum sickness (*Johannesen* et al), we do not consider it necessary to further discuss the curative effect of different sera From the time that the foreign serum was recognized as the damaging cause of serum sickness, attempts were made to free the anti toxin from the toxic substances The many efforts to produce a "pure" antitoxin have, until now, been unsuccessful

As *Ruffer* and *Daut* proved that the smaller the amounts were of injected

horse serum, the less frequently did the serum sickness symptoms occur, therefore the aim was to produce the necessary amount of antitoxin in the smallest possible dose of horse serum The attempts to find an artificial concentration lead to no practical results The reduction of the amount of serum to be injected can only be attained by using as many horses as possible for immunization, and by selecting for therapeutic use only the sera of those horses which are capable of producing relatively large amounts of antitoxin and neutralizing large amount of toxin

During the first years of serum therapy sera were used which contained only 20 to 50 antitoxin units in 1 cc , while now, by a suitable selection of horses, sera are produced, which contain up to 500 antitoxin units in 1 cc To provide, in an uncomplicated case of diphtheria of the pharynx, the 1000 antitoxin units that are necessary, previously 20 to 50 cc serum were needed, whereas to-day, with the use of serum with high antitoxin titre, only 2 cc are needed

That this influenced very effectively the incidence and intensity of serum symptoms, is seen in the statistics of Daut He found among 74 injections where the dose was 2 to 15 cc , 5 cases of rashes or 4%, in 28 cases injected with 20 to 60 cc of serum 32, 14% We have already mentioned that when injecting 100 to 200 cc serum, we found serum symptoms in 85% of the cases

To *Bujwid* we owe another prophylactic measure He discovered that the horse serum has a highly toxic effect directly after the removal of the blood from the veins of the horse

On the basis of his extensive statistics, *Hc* [illegible]
sickness depends mainly upon the individual [illegible]
Unruh believed that horse serum obtained [illegible]
intensive toxic and characteristic effects To what degree the explanation of *Bujwid* could prove the statements of *Hartung* to be right cannot be decided because *Hartung* does not mention the age of the individual sera

The most violent serum sickness which we observed (P Max) followed the injection of 150 cc serum, which was only 14 days old At that time as an exception we used sera of 4 different horses which were bled only 14-21 days previously All 4 patients showed remarkable similar intensive symptoms of serum sickness But the toxicity of serum seems to become stabilized after several weeks We also saw severe symptoms after injecting serum stored for over six months

According to the proposal of *Bujwid*, serum is stored a few months before it is released for commercial purposes

Another technical procedure reducing the toxicity is based on the observation of *Spronck* He found that serum which is heated up to 59° Celsius produces almost no rashes

In the State serotherapeutical institute (Prof *Paltauf*, Vienna) diphtheria serum is submitted to this procedure However all cases of serum sickness in

diphtheria and after immunization were produced by heated serum We also heated single doses of scarlet fever serum several times but we were not convinced of any differences in their toxic effect Only when fresh serum was used, did the heating seem to have an effect Along with the previously mentioned 4 severe cases a serum of the same age and the same source was injected after having been heated The child showed a considerably milder serum sickness

Probably the heating influences that part of the toxic substance which also gradually disappears when stored It must be also mentioned that the toxic substance is not destroyed by freezing nor by drying in vacuum A method to determine the toxicity of the serum even after the injection of a very small amount of serum consists of an injection in hypersensitive persons (see p 104) In our experiments recorded on page 71 dealing with immunization, 1 to 2 cc serum of different origin was applied, but we did not find distinct differences between normal and heated serum or between serum of *Hoechst* and *Vienna* Our experiments on this subject have not been concluded

In any event the prophylaxis of serum sickness consists in the first place in using the smallest possible amount of serum

But even when large doses are administered severe cases of serum sickness are the exceptions The statement of *v Ranke* is correct that *in comparison to the saving of the lives of many patients the after effect of serum can be quietly disregarded*

Chapter 2

THE REINJECTION

The Ability for Immediate Reaction

Those authors, who until now have studied serum sickness, did not pay special attention to the symptoms after reinjection, but dealt with them statistically and clinically in the same way as with the symptoms after the first injection Likewise it was only in the course of our observations that our attention was drawn to the important differences between first and reinjection, which exist, mainly in connection with the time of onset and intensity of symptoms

August Sch , 3½ years old admitted 10/11/02 with scarlet fever and tbc fungus of the right elbow joint On 10/11 injection of 200 cc polyvalent streptoccus serum (Paltauf) Thereupon the patient had no fever for 8 days On 10/20, the 10th day after injection, fever and urticaria set in which lasted several days 10/24-11/3, no urticaria but ' hectic" fever which we related to the fungus Our experience since that time taught us to consider the symtoms as surely due to serum sickness We wanted to find out whether the fever could again be stopped by a repetition of the serum injection Thus we injected on 11/4, 24 days after the first injection, 100 cc of the same polyvalent streptococcus serum into the skin of the abdomen The injection was made at noon, that evening the site of the injection and its neighborhood was to a wide extent edematous and showed diffuse redness Eruption of erythema also on other parts of the body The fever, which was in the first days 38 4°, did not fall, on the contrary it rose to 39 7° We first suspected an infection but no abscess developed, on the contrary the swelling of the area of injection flattened out within a few days However five to six days afterwards urticarial and small papular eruption appeared which were very similar to the eruption which we are used to see in serum sickness

The peculiarity of the case was that the same child who one month previously needed 9 days until it reacted to the serum with sickness reacted this time within a few hours

Shortly afterwards another case was observed which showed the difference in the reaction between first injection and reinjection even more strikingly

Whereas the serum sickness after the first injection appeared only after an incubation time of seven days, such an incubation time was entirely missing after the second injection These two cases, just reported induced *von Pirquet* to construct a theory concerning the nature of the incubation time which we shall discuss on the following pages At first it was necessary to collect more observations, which was carried out by *v Pirquet* at first with *Joseph Hertzka*, later with *Schick*, in order to find out whether the mentioned observations expressed a general biological law

Looking over older charts of the hospital we found similar observations, the importance of which we had not recognized

Heinrich K , 3 years old On 6/13/02 he received 100 cc scarlet fever serum On the 8th day (6/20) onset of serum sickness lasting to the 26th day 7/17 34 days after the first injection 200 antitoxin units in 1 cc diphtheria serum were injected into the left arm On the same afternoon urticaria, edema of the lips The next morning the arm is extremely edematous The swelling lasted several days

Alexandrine K , 9 years On 5/28/02 received 180 cc normal horse serum which has no effect on the course of scarlet fever On 6/8 (11 days after the injection) severe serum symptoms which lasted to 6/17 During the course of serum sickness 16 days after the first injection the child was immunized against diphtheria Again as in the previous case 1 cc diphtheria serum was injected into the right forearm On the following morning the skin at the site of the injection down to the wrist was swollen, very tender and vividly red so that we thought at first of erysipelas Redness and swelling disappeared in several days

Elisabeth K , 6½ years admitted with severe scarlet fever on 5/1/02 Injected 5/3 with 180 cc scarlet fever serum On 5/15 after the scarlet fever symptoms had [illegible] swelled no rash These

and painful edema developed on the skin of the abdomen which extended [illegible] genitalia and thighs and disappeared only after one week

Looking over the publication of Hartung we found two cases observed in the year 1895 where serum sickness appeared rapidly after the injection In the history Hartung himself mentions that the child had been previously injected with serum (The interval between the two injections was in case 2, 32 days, in case 8 23 days) We found a similar case in the publication of *Denys* and *Leclef* The dependence of the speed of the reaction upon the previous injection did not strike either of the authors Why does it happen that such a peculiar symptom was until now overlooked? If every reinjection would have been followed by immediate serum sickness one would have noticed it long ago It occurs however very frequently that children become infected several times with diphtheria and are injected repeatedly with serum Some sera as for instance the Tb serum of Maragliano or the Menzer serum against rheumatic fever are injected

every day or every week During this therapy certainly reactions occur frequently, but they usually are not diagnosed as serum sickness but as reactions between sickness and antitoxin *Aronson* already declared that the reaction to Menzer's serum was not caused by the content of antitoxin, but was due to the nature of the foreign serum The most important reason for the lack of reaction is the length of the interval between first and second injection, a point which we shall have to discuss later Another difference between our cases and the other above mentioned kind of reinjections is the size of the first dose of serum We inject between 100 and 200 cc serum, by using the present dosage of diphtheria serum the first dose amounts to only 5–10 cc But likewise as exanthemata etc appear after small doses of serum, so also such small amounts (1–1 2 cc) may provoke sensitiveness to the reinjection, as the following cases show, which were selected from a large number of reinjected diphtheria cases

Franz Z, admitted on 6/8/03 with measles, received for immunization 200 antitoxin units (1 cc) Discharged on 6/16, developed urticaria at home—the earliest on the 9th day after the first injection On 8/2, six weeks later, again injected against croup with 1500 antitoxin units (5 cc diptheria serum) Shortly afterwards generalized urticaria, edema of the face His sister, Frieda Z, reacted in a similar way She was immunized with 200 antitoxin units on 6/10 and again 6/26 as she was in the hospital with measles On 8/2 admitted with croup she was injected with 5 cc diphtheria serum One hour later her face became red and edematous The eyelids were so much swollen that the right eye could not be opened Two hours later generalized urticaria, temperature 38 6° Locally slight swelling and great tenderness

Elli M, 4 months old, first injection on 6/20/01 12 cc diphtheria serum (2000 antitoxin units) against diphtheritic croup On 6/30 sudden fever up to 39 0°, at the same time urticaria eruption (10 days after injection of serum) The fever lasted two days, later the rash became more morbilli-like and multiform in character and remained visible for several days Ninteen days after the first injection (7/9) was again injected with 5 cc (500 antitoxin units) diphtheria serum because symptoms of croup reappeared About one hour afterwards a severe general eruption of urticaria started From the site of the injection the skin of the entire abdomen became swollen In the afternoon the temperature rose to 39 5° there was no fever since the first reaction Frequent vomiting On the next day fever around 39 0° The area of injection shows [illegible] extends to the [illegible] were [illegible] Dis[illegible]er the [illegible]er and [illegible]ner of [illegible]theria diphtheria bacilli on 12/27 Therefore she was inje[illegible] serum (300 antitoxin units) 27 days after the first injection One hour after this injection distinct swelling of the right hand, which later extended over the whole forearm Twenty four hours later still distinct edema from the elbow joint down In the neighborhood of the injection distinct discolorization, small sized, indistinct pale rosy-red rash above the area of the injection up to the elbow joint

All 8 cases have *in common* that after the *first injection* of horse serum serum sickness developed at the *normal time*—between the 8th–13th day But when the same individuals were *reinjected* with horse serum after an interval of 16–42 days symptoms of serum sickness appeared *immediately*—that means at once or or at least rapidly within 24 hours

Experimental Studies

About the single cases reported until now the objection is possible that by chance a kind of serum was used for reinjection which produces more vehement symptoms and in a shorter time In order to counteract this objection we took advantage of an opportunity which offered itself to inject all children at the same time with the same serum when a case suspected of diphtheria occurred on the general ward and to observe closely its course in children injected for the first time and in those who had been previously injected

I Immunization on 2/11/03 At 6 00 p m injection of 1 5 cc diphtheria serum into the skin of the forearm Three children were previously injected

1 *Johanna J* 180 cc scarlet fever serum 31 days previously No definite symptoms of serum sickness

2 *Emilie K* circa 8 cc diphtheria serum 6 years ago and the same dose 36 days ago

3 *Dr v P* 200 cc scarlet fever serum 9 months ago, 8 days later urticaria and joint pain

Numbers 4, 5, 6, 7 were children not injected before 1 and 2 showed identical

half an hour itching, after one hour slightly red swelling of a radius of 2 cm The reaction of Dr v P is not an absolutely specific reinjection reaction such slight redness and swelling are also often seen after the first injection But the hard edema of the arm in cases 1 and 2 is specific

II Immunization on 3/7/03 Each patient received 1½ cc diphtheria serum

1 *Barbara T* 46 days previously injected with 100 cc Serum sickness started after the first injection on the 10th day and lasted to the 23d day

2 *Karl D* previously injected with 6 cc diphtheria serum on 2/7 and 200 cc scarlet fever serum on 2/15 He was still suffering with serum sickness on 3/7

3 *Rudolf J* Injected 4 days before with 200 cc scarlet fever serum Serum sickness started only on 3/14 So the reinjection occurred therefore within the incubation time

4 5, 6, not previously injected

Only Number 1 showed a typical sensitive reaction after 5 hours, analogous to cases 1 and 2 of the first series Among those not previously injected, two showed exanthemata but only 10 and 11 days respectively after injection i e starting at the normal time

Number 4 3/17 In the evening indistinct erythema 3/18 universal, multiform erythema, temp 38 2°

Number 5 On 3/18 erythema with large spots

These cases demonstrate clearly that the *same serum has different effects, depending upon whether or not it is acting on a previously treated organism* In the previously treated system it creates an immediate and violent reaction, in a person not previously treated either no reaction (Case 6) or a reaction at the normal time of serum sickness (case 4 and 5) Thus the objection is removed that the rapid onset of symptoms could be due to the use of a certain kind of serum for reinjection But why do Cases 2 and 3 not react who were also previously treated with serum? For case 3 the explanation lies in the interval between the first and second injection In all cases reported up to now which showed specific reactions two to six weeks had elapsed when the second injection was performed, but in case 3 the interval was only 4 days We shall discuss this point more thoroughly later

However in case 2 all conditions were present intensive preparatory treatment sufficient interval, and in spite of it no symptoms On the basis of the results of later experimental studies we shall see that this case is an exception to the rule for which we have no explanation

III Immunization on 10/30/03, each child received 1 cc diphtheria serum
1 case previous injection 150 cc serum interval 36 days
2 case previous injection 150 cc serum interval 32 days
3 case previous injection 200 cc serum interval 6 days
4 case previous injection 200 cc serum interval 4 days
5 case previous injection 200 cc serum interval 1 day
6 case previous injection 200 cc serum interval 1 day
7–12 not previously injected cases as control

Result Among the six control cases one showed local hives on the 7th day Cases 1 and 2 developed typical immediate infiltrations on the forearm Cases 4, 5, and 6 did not show any reaction Only case 3 developed on the day of injection a local erysipelas like redness of 3 cm radius, a reaction which may not be specific

The experiment reveals that 32–36 days after the previous injection of serum, specific sensitiviness was present, but is not yet present 1–6 days after the first injection

IV Immunization on 7/19/03 1 cc diphtheria serum into the skin of the forearm
3 previously injected cases
1 *Gisela H* 200 cc scarlet fever serum 39 days ago
2 *Karl B* 140 cc scarlet fever serum heated according to *Spronck* to 59° Celsius 56 days ago
3 *Johann S* 100 cc scarlet fever serum 6 days before
4–10 not previously treated cases (controls)

Result Not one of the 6 control cases showed any reaction nor did case 3 Case 1 [illegible] Case 2 weak
rs

So we see again that 39 days after the first injection of a large dose specific sensitiveness is present, but is not yet present after an interval of 6 days

V Immunization on 11/15/03 each child received 1 cc diphtheria serum

Name	Amount of serum	Day of onset of serum sickness after the 1 injection	Interval since the 1 injection
	cc	day	
1 Franz T	200	8th	6 months
2 Paula E	316	13th	41 days
3 Egon E	200	8th	38
4 Eduard G	100	9th	38
5 Anna R	200	7th	20

The circumference of the left forearm 19 cm of the right 16 cm Of the left upper arm 17 cm of the right 16 cm Temperature 37 5° In the left axilla one bean sized node In the right axilla just palpable glands

gland swelling on the same side later no symptoms

Case 1 No immediate local reaction but instead on the 7th day a mottled *erythema* extending over the whole external surface of the left arm Slight swelling of the axillar glands

Result The specific local reaction is present after an interval of 20 to 41 days after the first injection It is absent when six months have elapsed after the first injection (Case 1)

Let us now summarize the *results* of the 5 experiments

Among 30 children who had previously never received serum, only six (20%) developed distinct serum symptoms after an injection of 1 0 to 1 5 cc diphtheria serum but not earlier than on the 6th day An immediate reaction (local) comparable to previously described reactions did not appear Only in one child was after 24 hours a slight infiltration at the site of the injection still discernible

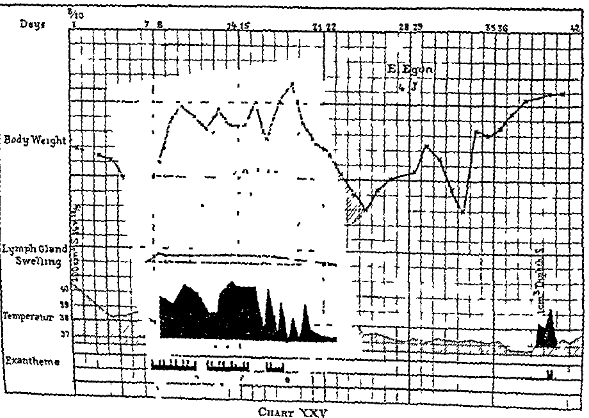

Days
8/10
1
7 8
14 15
21 22
28 29
35 36
42
E. Egon
4 J.
Body Weight
Lymph Gland
Swelling
40
39
Temperatur 38
37
Exantheme

Chart XXV

The 20 previously injected cases can be divided into three groups according to the length of the interval between the first and second injection

1 *Interval of 1–6 days six cases* No immediate local reaction with one exception (III/3) The child showed an erysipelas-like redness with a radius of 3 cm on the day of the injection The interval was 6 days

2 *Interval from 6–9 months 2 cases* One child (I/3) showed a light swelling of 2 cm radius one hour after the injection, a symptom which can also be seen in some cases after a first injection The other one (V/1) showed no immediate reaction, but an erythema on the 7th day

3 *Interval between 3–8 weeks Among the 12 children belonging to this group eleven developed an immediate local reaction* Several hours after the injection a more or less intensive tender swelling of the injected arm was observed Only one case (II/2) was entirely negative One case (V/3) showed, besides a local swelling an immediate general eruption of a rash which reappeared on the 6th day Regarding the series of our investigation and the eight previously mentioned cases, which showed the difference in the time of onset of the serum sickness after the first and second injection we can make the following statements

Due to a single injection of horse serum a change takes place in the reaction of the human organism to the reintroduction of the same substance, which obeys a definite law

1 *The serum sickness which usually starts after the first injection after an incubation time of several days appears within a few hours The incubation time is lost*

2 *Besides this difference in the time of the reaction a gradual change is observed The reinjected individual is hypersensitive He reacts more frequently even after an injection of small amounts (in the experiments 90% in contrast to 20%) and more intensively The reaction consists mainly of an intensive edema in the area of the injection, less frequently of fever and generalized exanthema*

3 *This altered reaction is observed regularly, if at the first injection large amounts of serum are used and if there is an interval of 2–3 weeks between the first and second injection (reinjection)*

The Accelerated Reaction

Until now we have devoted our attention only to the immediate reaction But one case of the experimental group (V) could have already at that time called our attention to the fact that the symptoms after reinjection are not exhausted with the immediate reaction

Egon E (V/3) First injection of 200 cc Onset of the first serum sickness on the 8th day After an interval of 38 days reinjection of 1 cc serum Immediate swelling,

universal exanthema In the next days no new symptoms On the 6th day *reappearance of generalized urticaria* (Chart XXVI) The following cases ran a similar course

Theodor H admitted with croup on 2/14/97 received on successive days (From 2/14–2/17) altogether ca 32 cc diphtheria serum 2/14–3/6 (16 days after injection) eruption of urticaria On 4/4/97, 49 days after the first injection, again injection of 1500 A U Immediately after the injection universal urticaria, 38 8° On the 6th day after injection (4/9) fever starts, lasting to 4/12 On 4/10 urticaria

Maria K On 9/19/02 1500 A U Serum rash after discharge (ca 12 days after injection) Then an interval of 4 months On 1/27/03 1000 A U in 8 cc serum Around the site of injection partly mottled, partly confluent redness and a few hives 2/2 (6th day) urticaria, 38 2°, joint pain

Anna G January 1903 injected in the Franz Josef's hospital against diphtheria Interval 2 months On 3/14/03 200 cc scarlet fever serum Local urticaria, edema at

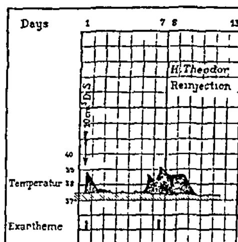


CHART XXVI

the site of the injection 9/18 (5th day) universal urticaria On the 10th–13th days joint pain, intensive edema again universal edema on the 12th day

This case will be discussed later more thoroughly (page 93)

Franz K 7 years admitted on Jan 1, 1901 with scarlet fever 1/4/04 cc diphtheria serum On 1/5 200 A U scarlet fever serum On 1/13 onset of serum sickness 9 or 8 days after injection urticaria spleen enlargement, swelling of lymph glands and edema Angle of the weight curve marks the beginning of the convalescence (on 1/25 21 days after injection) On 2/20, transferred to the Wilhelminen hospital on account of measles, where possibly another prophylactic injection of serum against diphtheria was given

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p.m till morning *frequent vomiting* sleeplessness, thirst 4/18 in the morning sneezing several times At the round brightred maculae with indistinct central hives scattered all over the body Conjunctiva injected Towards evening another eruption of rash 4/19 the urine contains a trace of albumen, today for the first time Today the weight is at its maximum Circa 400 grams of edema

Shortly before injection and ½ 3, 6, 8 and 10 days afterwards blood is withdrawn and tested for precipitation (microscopically) with rabbit anti horse serum and on the other hand with horse serum (½)

TABLE 3

	Before injection	½	3	6	8	10 days after
Precipitation with anti horse serum	+	++	++	++	++	++
Precipitation with horse serum	+	weak	trace?	+ exanthema	++	++

What these cases have in common is that, after an immediate reaction, several days of complete latency follow, which period is concluded by an eruption of new symptoms on the 5th or 6th day We encounter here again an incubation period which shows a substantial difference from the incubation time after the first injection, *it is shortened* Another peculiarity, which we shall discuss later more thoroughly, is revealed in the clinical picture the accelerated reaction sets in with violent, frequently stormy symptoms, and is terminated more rapidly than the normally timed reaction after a first injection A short incubation time can be observed sometimes after a first injection Fourteen cases among 90 showed the onset of generalized symptoms on the 6th or 7th day after injection However in cases of reinjection, late symptoms, if they occur at all always appear on about the 6th day after injection If an individual, whom we know has already once been injected with serum, shows no symptoms by the 7th day after injection, we need have no fear of serum sickness If however, serum sickness starts on the 6th day in a child whose previous history is not known, one cannot conclude with certainty from the length of the incubation period alone, that the child was previously injected Only the combination of a shortened period of incubation with a sudden onset and rapid termination of the disease gives the typical picture of an *accelerated reaction* of a reinjected individual

The double picture of the "immediate" and "accelerated reaction" leads us to a third form of reaction observed in a reinjected person, which consists of the accelerated reaction only The immediate reaction is left out This picture is seen after a *reinjection* following a *long interval*

Emma Sch was admitted on 9/25/02 with croup and received 12 cc diphtheria serum Till 10/12 no symptoms 7 months later on 4/11/03 injected with 6 cc diph

theria serum From 4/12–4/16 no fever On 4/17 (the 7th day) 37 8°, and universal urticaria

Oscar W 11 years First injection in the beginning of 1904, 1 cc given as a prophylactic dose on account of diphtheria of his brother Second injection on 9/25 (*9 months later*) 10 cc (3000 A U) on account of severe pharynx diphtheria 9/30 (5 days after injection) eruption of urticaria which quickly disappears 10/1 in the afternoon (6 days after reinjection) generalized urticaria On 10/2 in the forenoon large areas of redness with occasional hives over the entire body No fever

Anna K , 3 years First injection on 9/3 against diphtheria 4500 A U (18 cc) Hospitalized 23 days, no serum sickness 2nd injection on 3/3/05 (*18 months later*) 3000 A U in 12 cc serum On the next day the site of the injection is only tender but not red nor infiltrated *Early on 3/9, 5½ days after the injection*, violent eruption of

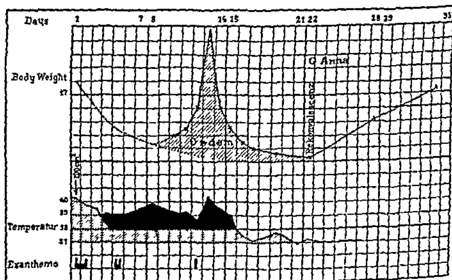


CHART XXVII

urticaria on the entire body, starting from the site of injection *The inguinal glands, particularly near the site of injection, tender and enlarged* In the afternoon 37 5°, no further symptoms

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8 cc diphtheria serum (1000 A U), 6/10 (7th day) eruption of large urticaria in the crural region, smaller on the rest of the body

What is really the reason that one time an immediate reaction develops, another time an accelerated reaction, and another time both kinds of reaction?

The experience that when the injection is made after a long interval, the immediate reaction fails to appear, leads to the idea that the *decisive factor is to be sought in the time which elapses between the first and second injection.* A chart (table 4) containing all the results of the reinjection will corroborate this assumption

In this chart only those cases are included which developed a positive reaction after the second injection The cases receiving several injections were not considered, because they would have caused complications in the arrangement according to the duration of the interval

We see that, according to the length of the interval between the first and second injections, three periods can be differentiated, which overlap each other

1st interval of 12 to 40 days immediate reaction alone

2nd interval of 1½ to 6 months immediate and accelerated reaction

3rd interval of over 6 months only accelerated reaction

That these periods are not sharply separated, can be discerned with the first glance at the chart The gradual transition, as well as the distribution of the forms of reactions are illustrated by the spectrum shown in Chart XXVIII

The immediate reactivity sets in regularly 12 days after the first injection and is characterized usually by local edema, less frequently by generalized symptoms Only one positive case stands out in comparison with numerous negative cases within the first 12 days This one case showed, after an interval of 6 days, erysipelas like redness at the region of the injection After an interval of 3 months and more, the immediate reaction is no longer obligatory, then gradually decreases in frequency However, isolated cases also occur even later The longest interval after which an immediate reaction appeared was 3 years

Marfan (Soc med 5/26/05) also reports a case of immediate reaction after a 3 year interval This restriction of the immediate reaction to a relatively short time explains why this observation could have been overlooked for so long a time Most of the cases treated with serum up till now were diphtheria cases, if reinjections were administered they were given during the first days of treatment before the onset of sensitiveness If the reinjection was made somewhat later, at the time usual for serum symptoms, the immediate reaction coincided with the symptoms appearing at the normal time due to the previous injection and could therefore

TABLE 4

Name or No	Amount 1st Inject	Onset 1st Serum Sickness	Interval	Amount of Serum Reinjection	Immediate Reaction		Accelerated Reaction
					Local	Universal	
			days				
III/3	200 Sc		6	1 Di	+ ? redness		
W Friedrich	Di	?	12	150 Sc	+ strong	urticaria	
P	200 Sc	5th day	12	100 Sc	+		
No 18	Di	?	14	15 Di	+		
K Alexander	180 N	12th day	16	2 Di	+ strong	+ 2 days	
No 60	8 Di	?	16	10 Sc	+	+ 2 days	
M Elly	12 Di	11th day	19	5 Di	+ very strong		
K Elisabeth	180 Sc	13th day	19	50 Sc	+ very strong		
V/5	200 Sc	7th day	20	1 Di	+		
No 23	3 Di	?	21	6 Di	+		3rd day
Sch August	200 St	11th day	24	100 St	+	+	
No 22	370 Sc	14th day*	24	50 Sc	+ strong	+	
W Josef	8 Di	12th day	27	16 Di	+ weak	+ collapse fever	
No 7	30 Di	?	28	2 Di	+ ?		
No 29	1 Di	?	29	1 Di	+ weak		
H Augustine	Di	?	29	150 Sc	+ very strong	+ 8 days	
St	1 Di	Ø	29	1 Di†	+ weak		6th day
I/1	180 Sc	11th day	31	1 5 Di	+ strong	+ 4 days	
III/2	150 Sc		32	1 Di	+ strong		
K Heinrich	100 Sc	9th day*	34	2 Di	+ strong	+	
III/1	150 Sc		36	1 Di	+ strong		
V/3	200 Sc	8th day	38	1 Di	+ strong		6th day
No 28	200 Sc	12th day	38	1 Di	+ weak		
V/4	100 Sc	9th day	38	1 Di	+		
IV/1	200 Sc	12th day	31	1 Di	+		
V/2	316 Sc	13th day	41	1 Di	+ strong		
No 5	Di	?	42	10 Di	+		
Z Franz	1 Di	?	42	5 Di	+	+	
II/1	100 Sc	10th day*	49	1 5 Di	+ strong		
No 14	c40 Di	+	49	10 Di	+		7th day
H Leopold	100 Sc	8th day*	50	2 Di	+	+	
G Anna	Di	?	60	200 Sc	+		5th day, severe
P Irene	1 Di	Ø	60	100 Sc	+ very strong	+	6th day, lasting 8 days

No 6	20 Di	?	60	10	Di	+		
IV/2	150 Sc†	ø	60	1	Di	+ weak		
F Franz	200 Sc	10th day	90	18	Di	+ ?		6th day
No 11	10 Di	13th day	120	10	Di	+		6th day
No 1	10 Di	?	120	10	Di	ø		6th day
K Marie	8 Di	12th day	120	8	Di	+ weak		6th day, urtic , joint pain
No 43	18 Di		120	8	Di			4th day, local
			months					
M Anna	5 Di	?	5	6	Di	+	+	
V/1	200 Sc	8th day	6	1	Di	ø		7th day erythema
No 26	12 Di	?	7	6	Di	ø		7th day
W Oskar	1 Di	?	9	10	Di	ø		6th day, urticaria
No 12	20 Di	15th day	9	20	Di		+	7th day
No 3	Di	?	9	20	Di			5th day, local
Dr v P	200 Sc	9th day	9	1 5	Di	+ weak		
H Alfred	8 Di	?	14	50	Sc‡			8th day
K. Anna	18 Di	ø	18	12	Di			6th day, violent urticaria
C Karoline	20 Di	ø	18	10	Di			6th day, urticaria
B Johann	Di	?	18	5	Di			8th day, exanthema
No 4	Di	?	18	30	Di			6th day, fever 8th urtic
			years					
No 63	2 Di	?	2	8	Di			7th day urticaria
L. Josefine	Di	?	3	11	Di			7th day urt lasting 2 days
No 13	10 Di	?	3	2	Di	+		
P Johann	10 Di	?	3	20	Di	ø		6th day erythema
No 2	Di	?	4		Di			5th day
Z Hermine	16 Di	ø	4½	8	Di			7th day gen urtic
L Robert	16 Di	?	5	10	Sc	ø		8th day gen urtic
G Johanna	15 Di	ø	5	200	Sc	ø		6th day very violent
K Valerie		ø	7½	200	Sc	ø		5th day lasting 8 days

Sc—Scarlet fever serum Di—Diphtheria serum N—Normal serum St—Polyvalent streptococcus serum
* Severe
† Heated
‡ Frozen

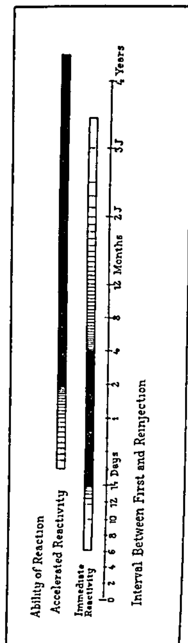


Chart XXVIII

not be separated from those symptoms Later reinjections at the time of the highest sensitiveness, 20–50 days after the first hardly ever occur in diphtheria The first disease (diphtheria) is, at that time, terminated and the child is protected against a new infection through his immunity created by the first attack of diphtheria

Only after loss of this immunity may reinfections with diphtheria occur occasionally At this time the organism is already in the third period, and therefore no longer reacts immediately but shows an accelerated reaction

The difference between an accelerated and a normal timed reaction is all the more easily missed as the first reaction occurs not infrequently around the 6th day A comparison with an early reaction in the same individual, where we started is possible only in few cases The accelerated [illegible]

period of accelerated reactivity Even after $7\frac{1}{2}$ years the accelerated reac tion was still to be seen

Clinical Symptoms Following Reinjection

I The Immediate Local Reaction—The Specific Edema

Let us once more look over the clinical symptoms, which represent the specific signs of the reaction of a reinjected individual We must consider the immediate and accelerated serum sickness and distinguish in the immediate reaction local and general symptoms

A very carefully observed case should illustrate the specific local reac tion

Dr v P Previous injections 1902, 200 cc scarlet fever serum 1903, 5 injections together amounting to 29 cc diphtheria serum 1/21/05 injection of 15 cc antitetanus serum into (the skin) of the left forearm The swelling produced by the injection [illegible] 0–10 cm , is [illegible] pots Pain [illegible] 37 4° The [illegible] re, the skin [illegible]

Spontaneous pain less than yesterday Pain on pressure [illegible] ference 32 cm The length of the swelling 28 cm 30 hours after the injection Circumference 33 cm

3d day Itching On the diffusely red swelling appear suddenly quickly passing pale spots (indistinct hives) Circumference 31 cm

4th day Itching and hives like yesterday No general symptoms The swelling is

softer, less reddened, but slightly pigmented During the following days diminution of the swelling

8th day Swelling has disappeared Slight pigmentation Daily examination of the blood for 14 days reveals no formation of precipitin

We have here an individual strongly prepared with several injections of large amounts of serum who, one and a half years after the last injection, still reacted with specific edema The characteristic trait of the specific edema lies in the circumstance that the swelling produced by the injection of serum does not disappear, but gradually changes to an edema which becomes more and more intensive Notwithstanding, horse serum is absorbed and reaches the circulation This can be proven by testing the serum with rabbit—antihorse serum

The amount of the additional accumulation of fluid in the edema can be determined by measuring the replacement of water This we did in one case The amount can be approximately determined by measuring the circumference of the forearm and the length of the swelling

At the time of the maximum of the swelling (after 30 hours) the circumference of the forearm amounted to 33 cm compared to 26 5 cm before the injection, the length of the swelling was 28 cm The additional mass h $(r^2\pi - r_1^2\pi)$ which results in about 800 cc of edema In place of the injected 15 cc we find an accumulation of fluid which amounts to more than 50 times the volume of serum injected

In H , a case which we shall describe later where the serum was injected into the thigh the difference between the two thighs was 5 cm (28 23) The length of the swelling was 20 cm The calculation gives an amount of 400 cc edema The injected 5 cc increased 80 times

Let us make an analogous calculation of the amount of edema in the experiment V/3 The whole arm becomes edematous after an injection of 1 cc diphtheria serum

So we see that a constant proportion between the injected amount of serum and the edema does not exist That the proportion can not be a constant one is proven by the fact that in many cases the specific edema is not so intensive, but extends to the next surrounding neighborhood of the site of the injection (See the series of experiments)

The effects of two serum injections given to Dr v P will illustrate this

He received on 2/21/03 8 cc diphtheria serum into the left forearm, 9 months

mented An even milder effect was produced by the previous injection on 3/11/03 after injection of 1½ cc serum After ½ an hour itching, after one hour a slightly red swelling measuring 1 cc in radius

These slight reactions cannot be distinguished in the individual cases from the slight redness and swelling as they also occur after a first injection in the neighborhood of the site of injection Such symptoms can be seen also after injection of varied substances, even after injection of physiological NaCl solution

The judgment of the amount of edema is easier if after injection of a small amount of serum—as in our experimental series—1 to 2 cc—an intensive swelling develops The greater the amount of serum injected the more difficult it becomes to determine the absolute increase of the local swelling

Friedrich W 16 months First injection on 11/17/03 against diphtheria Second injection on 11/29 on account of severe scarlet fever with 150 cc scarlet fever serum Interval 12 days After 14 hours the abdominal wall around the site of the injection intensively infiltrated extended 11 27 cm, with a sharply defined margin The edema has a volume of 600 cc , if we assume that the infiltration has a height of 2 cm The volume of the injected fluid is therefore increased three times The skin over the edema is slightly yellowish Scattered over the entire body red spots appeared with pinhead sized hives After 1½ d
extended downwards t
body In the evening
injection

We once saw a similar picture in a child who was never injected before (according to the statement by the parents)

Gustav P 11 years Admitted on 3/16, at the hospital until 5/3/04 On 3/16 injection, due to a medium severe scarlet fever, of 150 cc scarlet fever serum into the abdominal wall Previously had never had horse serum 12 hours later the area of injection very tender and edematous The edema extends to the skin of the back and is surrounded by a 2 cm wall like brim During the following days the infiltration flattens out, while it simultaneously extends in the width towards the thigh and back Thereby no rash develops, only a mottled, indistinct redness on the skin of the abdomen and of the back over the swollen parts and their surrounding area On 3/20 the edema has disappeared No further symptoms of serum sickness

Is this a case of specific edema in a child injected for the first time? In favor of this assumption is the fact that no late symptoms developed after the immediate reaction This would be, therefore, a case which acts primarily like a child who had been reinjected

Only one circumstance prevents us from recognizing this exception implicitly, that, namely, such a reaction was never observed in a child injected for the first time, when small doses of serum were used Furthermore not one of our 30 control cases, and none of the hundreds of diph-

theria cases showed such an edema after an injection of a small amount of serum, which could have been mistaken for a specific edema If one injects a large amount of serum into the abdominal wall, it is sometimes difficult to decide whether the edema is a specific one On this basis we restrict our diagnosis of a specific edema only to cases which, *after an injection of a small amount of serum (1–10 cc), develop a disproportionately large swelling* Particularly suitable for this are cases which were injected with 1 cc serum in the forearm where the edema appears 12 to 20 hours later, extending from the wrist joint to the elbow joint, and the skin is pale or slightly red As long as the swelling increases, the arm is exceedingly painful The spontaneous sensitiveness diminishes as soon as the swelling has reached its maximum The pain on pressure lasts for a longer time The swelling starts actually from the moment of injection, increases slowly, reaches its maximum about 24 hours later, and disappears entirely within 2 to 5 days Sometimes a small swelling and tenderness of the regional lymph nodes are present

We separate the immediate general symptoms from the local edema, in so far as they manifest themselves by an eruption of generalized exanthemata Certain insignificant general symptoms as feeling chilly or a slight rise in temperature are always connected with intensive local edema It is very exceptional to observe local necrosis after reinjection in human beings, a reaction not seldom seen in repeatedly reinjected rabbits (*Arthus*)

An example of this is the following case

Josefa Str 1st injection 11/9/94 10 cc diphtheria serum Second injection 10/13/97 1 cc diphtheria serum for immunization In spite of it the child developed diphtheria and received a third injection on 10/19 again about 8 cc diphtheria serum (1500 A U) On the next day the area of injection on the abdomen is painful The face is slightly puffy On 10/22 another injection of 8 cc (1500 A U) Two hours afterwards a hemorrhagic area measuring 2 cm developed above the site of the injection The surrounding skin is very tender and swollen In the evening the swelling extends to the upper left side of the abdomen extremely painful Temperature 39 4°

10/23 At night very restless Pain in the abdomen nausea rapid respiration [illegible] yellowish brown [illegible] r large

2 The Immediate General Reaction

We call the appearance of fever, exanthemata and other general symptoms developing within the first 24 hours after reinjection, an immediate general reaction It does not exclusively occur in reinjected persons, but in rare instances after a first injection It seems that adults show these early symptoms after a first injection more frequently than children Amongst numerous cases of serum sickness after a first injection we were able to find only two such cases in the children's hospital, whereas among the

adults whom Dozent *Pilcz* had injected with horse serum, several reacted on the first day with fever Nothing was known of a previous injection in any one of the cases

On what this sensitiveness to horse serum, known as an idiosyncrasy, of an individual not previously injected depends, we are not able to explain It has most likely nothing to do with the sensitiveness acquired by a previous injection These exceptions do not break the general law of the altered reactivity The cases from which we draw our conclusions are

A typical example of a fully developed, immediate general reaction is the following case

he was
ral of a
3/23/04

the child was admitted to our diphtheria ward and was injected with ... diphtheria serum for immunization The interval between the previous and present injection could not be determined Immediately after the injection the patient started to scratch At the site of the injection a hand-sized urticaria appeared other densely arranged hives with confluent halos broke out over the entire body The face was puffy Intensive itching During the course of the day the patient vomited several times

At 3 00 p m —the injection was given at 10 00 a m —no hives were any longer visible but i
still more e
hemorrhagi

We see here symptoms similar to the symptoms in the case Leopold H , page 68, and Heinrich K , page 69, representing the generalized immediate reaction a very acute onset of generalized urticaria resembling eruptions seen in cases of idiosyncrasy against chemical drugs

The eruption of urticaria starts almost simultaneously at the area of injection and on the other parts of the body, accompanied by intensive itching ... the face especially on the lips and
a The
case a
ia and

afterwards a erythematous eruption sets in of indefinite character So rapid a change in the form of the rash is not seen in the serum sickness with a normal incubation time It makes the impression that the symptoms, which otherwise require 8–14 days for development, were condensed into 24 hours No albuminuria was observed during the immediate reaction

Fever is a very frequent symptom The behavior of the temperature is similar to the fever of the tuberculin reaction After an injection made in the forenoon, the fever usually starts already in the same afternoon (August Sch 39 7°, Theodor H 38 8° Leopold H 38 2°) If the injection is made in the afternoon the fever usually develops on the next day (Emilie K 38 8°, Herman K 39 2°) In one instance we saw a *condition resembling collapse* as an immediate general reaction This collapse reminds us of those severe states of collapse leading to death, which *Arthus* described after intravenous reinjection of horse serum in rabbits The possibility is not excluded that in this case the serum was injected into a vein, the sub cutaneous hemorrhage at the site of the injection would indicate this as having occurred From this observation the general rule should be deduced that intravenous injections of serum which have often been recommended particularly in England and France can be perilous if they are given to a person previously injected with serum As we are frequently unable to exclude with certainty a previous injection of serum, we advise most urgently against the intravenous injection of serum

Josef W On March 4th admitted with croup after measles received 8 cc diphtheria serum (1500 A U) discharged on March 8th On March 20th the child developed a multiform erythema On March 30th readmitted with diphtheritic croup March 31st injection of 16 cc (3000 A U) diphtheria serum 27 days after the first injection The injection was made at 10 15 a m into the right abdominal wall 10 minutes later redness and urticaria eruption appeared around the area of injection Shortly after wards hives appeared on the face and were scattered over the body *15 to 20 minutes after the injection the child who was very well before began to vomit to roll his eyes his extremities became cyanotic his pulse could not be felt Flow of saliva* After application of stimuli and hot packs the patient gradually recovered from this collapse Until 3 o clock in the afternoon several eruptions of hives In the afternoon fever rises to 38 4° Next m[illegible]
a deep subcutan[illegible]
intravenously) [illegible]
The inguinal lymph nodes protruding larger than on admission

4/2 temperature 38 0° 37 5° (2 days after reinjection) The region of the s te of injection hemorrhagic Inguinal lymph nodes as yesterday 4/3 (3 days after in jection) 37 9° 37 6° no rash Three bean sized lymph nodes in the right inguinal region and several smaller ones on the left side one bean sized and several smaller nodes distinctly swollen On admission on 3/31 the inguinal glands were pea sized 4/5 (5 days after injection) In both inguinal regions a date sized pack of lymph nodes and several smaller lymph nodes 37 5° 37 3° 4/6 (5½ days after injection) 37 6° 37 8° During the night eruption of a morbilli like rash on the stem and face leaving the back free In the morning only remnants of the rash In inguine (right) three bean [illegible]

Whether actually there has been a death among human beings due to intravenous injection of serum we do not know The fatal cases of the

literature (Gottstein etc) refer to cases injected for the first time We believe that it is impossible to ascribe them to serum because after subcutaneous *first* injections of serum of even the largest doses we never experienced syncopal symptoms

The immediate general reaction is usually terminated within 24 hours if small doses are injected, however sometimes they last longer

Augustine H 3½ years Previous injections with diphtheria serum on 9/25 and 11/1/04 On 11/30 admitted with scarlet fever On the same day (29 days after the last

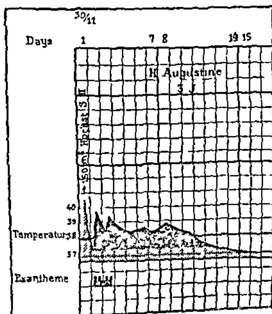


CHART XXIX

injection) 150 cc scarlet fever serum Hoechst Within a few hours a dense *generalized eruption* developed consisting of slightly elevated pea sized maculae On the right side of the abdomen (site of the injection) appears a very tense hard and painful *infiltration* with a slight redness of the skin extending down to the genitalia (labia) and down the back to the spinal column to the left to the mamillar line Hand and finger joints painful when moved

O

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38

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day on no fever

This case shows that local edema and immediate general reaction do not exclude each other, but may exist at the same time (See also Egon E, page 75, and the chart of reactions pages 80 and 81)

When the above mentioned Georg K received another injection, the local reaction was likewise combined with a general reaction which lasted three days

The boy was again reinjected on 4/9 17 days after the described reinjection, with 5 cc (1500 A U) on account of an exudate on the tonsils, which showed diphtheria bacilli in the culture At 8 15 in the morning an injection into the left thigh At 9 o'clock a great deal of thin secretion flows from the canula Face slightly puffed cyanotic *The region of the injection is more prominent than immediately after the injection* and surrounded by a palm sized redness At 12 o'clock temperature 39 3° (the boy had fever during the last days due to his larynx affection up to 38 3°) In the afternoon an intensive swelling of the thigh develops which was very painful

Not until the next morning (24 hours p i) did an urticaria eruption start which lasted 1½ days With this the general symptoms are exhausted

On the other hand the local affection was present for eight days

4/10 The left thigh is pale livid, intensively edematous, as if a large hematoma of the muscles were present The circumference of the left thigh is 28 cm compared with 23 cm of the right thigh

4/12 The circumference of the thigh 27 23 cm Around the area of the injection a greenish suffusion measuring 6–4 cm

This time a much more intensive local reaction developed than at the first time But the serum sickness was terminated with the immediate reaction whereas the first time an accelerated reaction followed, which will serve us, in what follows, as paradigma

3 The Accelerated Reaction

We call a reaction accelerated, if it appears in a reinjected individual 5–7 days after the reinjection This form of reaction can be distinguished on the one hand from the immediate reaction of a person injected for the first time by the shortness of its incubation period

The above mentioned George K was reinjected on 3/23/04 and developed an immediate generalized reaction This reaction was already terminated by 3/24 *During* the following days no symptoms On 3/27 the 5th day p i in the morning patient was still well Temperature 37 1° At noon very weary at 4 00 p m 39 5° at 8 00 p m swelling of the face develops particularly of the lips and eyelids, at the same time urticaria on the face neck, and thighs Slight swelling of the axillar lymph nodes No albumen No further symptoms

The sickness starts on the afternoon of the 5th day with a stormy aspect and is already terminated on the same evening As mentioned before this precipitated course combined with the early onset is pathognomonic *for a*

reinjection Several times we were able to recognize only from the clinical picture of an accelerated reaction, that the patient had been previously treated with serum In the case of an accelerated reaction the same symptoms occur as in a normal reaction after a first injection fever, various types of rashes, joint pain, edema

Anna G (Chart XXVII) 1st injection Unknown amount of serum on account of diphtheria 10 weeks before

2nd injection on 3/14/03, 200 cc scarlet fever serum on the third day of a severe case of scarlet fever Immediate local reaction The injection was made at 11 00 a m At 4 o clock in the afternoon mottled redness appeared at the site of the injection in the evening this area is enormously painful urticaria on the abdominal wall After 20 hours intensive edema and a local papulous eruption

5th day Universal urticaria which rapidly disappears

11th day Urticaria edema of the fingers

12th day Joint pains Hands, especially the fingers edematous Gain in weight *circa 400* grams

13th day Maximum of body weight (1200 g edema) Indistinct red spots on the stem From now on the edema decreases rapidly and has disappeared on the 16th day No albumen

4/7 third injection Thirteen weeks after the first three weeks after the second injection Patient receives 1 cc diphtheria serum (Behring) Mild specific edema which is still visible after 48 hours

A typical example of the course of an accelerated reaction is represented in the case of Johanna G This case is all the more remarkable as the interval between the first and the reinjection amounted to $5\frac{1}{2}$ years In the case of this patient we made daily *leukocyte counts* It was interesting to see that at the time of the accelerated reaction an intensive drop in the number of leukocytes occurs This drop corresponds to the drop of the leukocyte curve during the normally timed reaction after the first injection (Compare Charts XXX and XXXI) Also in the curve of the leukocytes is indicated the character of the accelerated reaction of serum sickness Acute onset at an earlier time, intensity, and rapid termination

ant 1 as scarlet

any symptoms of serum sicknc

10/29/03 received at 9 30 a m

diphtheria serum for immunization

noon towards evening a rapid pulse

n vomiting At 5 30 p m still

hemorrhages, caused by scratching On the other parts of the body indistinct remnants of a rash One would think that one was looking at a skin devastated by a 3 to 4 day continuing erythema exudativum On the abdomen some small hives with large halos Distinct swelling of the regional lymph glands in inguine and of one thoracal lymph node *Afternoon temp* 37 8°

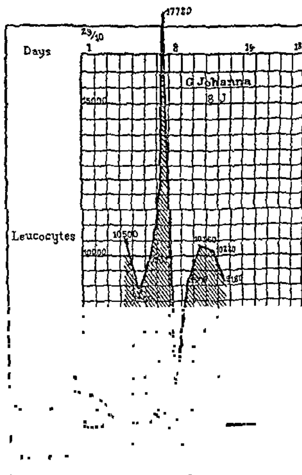


CHART XXX Leukocyte count after reinjection

8th day In the morning still 37 3° from then on no fever, exanthema disappeared

Leukocyte count	4th day	10 500
	5th day	8 900
	6th day	9,900
	7th day	17,780
	8th day	5,720!
	9th day	9,280
	10th day	10 300
	11th day	10,220
	12th day	9,180

The following case illustrates the behavior of the lymph glands during an accelerated reaction

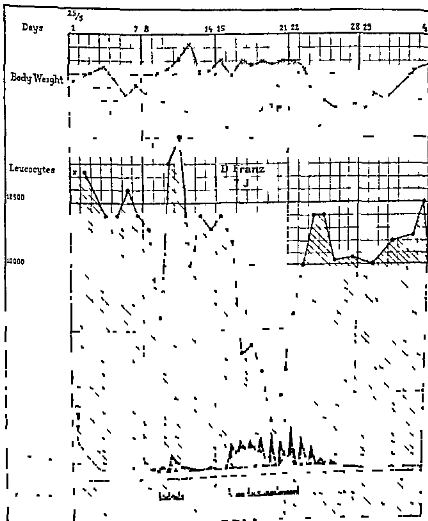


CHART XXXI Leukocyte count after first injection

Anna R 5 years 10/25–12/13/03 In the spring of 1903 diphtheria treated with [illegible] 200 cc scarlet fever serum into the right [illegible] glands [illegible] zed right several bean-sized [illegible] uding
Confluent in the shape of a sausage and [illegible]
5th day Inguinal glands increasing in size

6th day Inguinal glands on the right side still larger In the afternoon towards 3 00 an eruption rather generalized urticaria

7th day Strong desquamation of the skin, many effects of scratching, isolated pea-sized hives surrounded by red halos

8th day Inguinal lymph nodes, right bean-sized, left smaller

10th day Inguinal lymph nodes, right in a shape of a sausage, bean-sized

11th day The glands in inguine both sides less than bean-sized, not longer like a sausage

21st day Injection of 1 cc diphtheria serum Slight swelling at the site of the injection and a mild swelling of the regional lymph nodes

The inguinal lymph nodes are distinctly enlarged already 3 days after injection, they decrease in size from the 10th day on The large amount of serum (200 cc) was disposed of with only insignificant symptoms Similar enlargement of the glands is seen in the case of Robert L Here the interval between first and reinjection amounts to 5 years

Robert L 11/21/03–1/3/04 Was in the hospital 5 years ago (April 15, 1898 for 12 days) Two to three days after discharge a morbillous exanthema On 11/22/04 injection of 10 cc scarlet fever serum into the right side of the abdomen

8th day Inguinal lymph nodes on the right side until now bean sized today they became sausage like protruding bean and larger than bean sized left bean sized Ad nates indistinct net-like erythema

9th day Temperature 37 3°–37 0° Remnants of exanthema on the right side of the abdomen There is a group of fresh hives with large halos, scattered hives on different parts of the body

10th day On the right side of the abdomen pale red, separated spots No fresh hives

11th day No fever, lymph glands as they were on admission

It is remarkable that in this case the incubation time after the reinjection seemed to be shortened in comparison to the reaction after the first injection of the same individual, but that its duration is nearing the normal incubation time

Whether or not the accelerated reaction persists throughout the whole life, or if it exists only for a limited time, we can not as yet decide, we have just a little experience as to whether the accelerated reactivity through an always increasing incubation time returns to a normally timed reaction or if the accelerated reaction later in life disappears in the same manner as we learned it happens to the immediate reaction and that instead of it the normal incubation time returns

The decision of this question will only be possible after a larger number of years will have elapsed since the introduction of serum therapy

Diagnostic Significance of the Immediate and Accelerated Reaction

We have already discussed repeatedly the characteristic form of a reaction of a reinjected person with the idea in mind, that from it retrospectively

we would be able to diagnose a previous treatment of the person with horse serum

This conclusion is only permissible if the result of the reaction is positive If the immediate reaction does not take place one can not conclude that no previous treatment has been carried out Some individuals are not sensitive to repeated injections just as there are individuals who do not react visibly to the amount of 200 cc serum

Agnes T admitted four times to the diphtheria ward was injected on 3/22/98 after 2 years on 10/17/00, again 15 months later on 1/13/0? and finally after a one month interval on 2/22/0? No distinct reaction was observed after any of these injections

But the opposite we can tell with certainty that everybody who develops a specific local edema, or a typical rapidly appearing accelerated reaction must have been previously injected From this the practical value of these forms of reactions becomes apparent

Its significance will be enhanced by the following there are persons who do not react clinically to the first injection of horse serum but who behave at the reinjection like persons who reacted after the first injection This finding corresponds to the behavior of rabbits Their first serum sickness runs a symptomless course whereas they show the typical local edema after reinjection

We can conclude from this that our methods of observation are insufficient to establish the existence of the first serum sickness The disease did not reach the threshold of clinical perceptibility whereas certainly biological alterations must have occurred

Accidentally in an experimental study next to other previously injected children we injected a child as control who presumably was never before injected We were surprised to see that this child likewise showed an immediate local reaction It was revealed later that 29 days ago this child had been immunized on account of diphtheria of his siblings

Franz W
4/7 (interva
swell ng of t
t on persisted for 2 days

We possess therefore in the immediate or accelerated reactivity a new cri

for
tox

of the human to *revaccination* The accelerated and modified reacti... smallpox vaccine proves a previously successfully performed first vaccination

Chapter 3

THEORY OF SERUM SICKNESS

Formation of Precipitin In Vitro Provable Antibody Reaction

On the preceding pages we have limited ourselves to clinical observations and have purposely avoided mingling our theories with the facts The difference in the reactivity between the first injection and the reinjection forced us to the formation of some theoretical explanations of this difference This *difference could not be due to the antigen (injected serum)*, as we have shown in our experiments since the same serum caused different kinds of and differently timed reactions depending on whether it was injected into the organism for the first time or was reinjected Thus we came to the conclusion that it was the human organism which has become specifically altered due to the first injection of a foreign serum and that it has acquired a new property in consequence of which the second reaction occurs more quickly than the first

We now ask ourselves what kind of alterations developed in the organism after it was injected with a foreign serum We know from the results of biological research that specific substances are formed in the injected organism When these substances are brought in contact with the antigen in a test tube they bring about a precipitation

We owe the discovery of this substance called precipitin to R Kraus who demonstrated that the serum of an animal immunized against typhoid fever produces a precipitation when in contact with the germ free filtrate of a typhoid bacilli culture Furthermore it was found that the serum of animals which were previously injected with the serum of a foreign animal produced a precipitation when in contact with the antigen (the serum used for the previous injection)

Tschistowitsch observed that the serum of a rabbit previously injected with horse or eel serum shows a precipitation if brought in contact with horse or eel serum An analogous report was made by *Bordet* about rabbits which had been injected with hen serum

The formation of precipitin is a specific reaction similar to that of the formation of immune bodies This was made clear even in the first publications *Bordet Uhlenhut* and *Wassermann* used it for the forensic differentiation of the different kinds of blood *Nuttall* used it for zoological differentiation

Hamburger and *Moro* were the first to prove that humans also form precipitins after an injection of horse serum These authors expressed their assumption that the symptoms of serum sickness are due to the

appearance of precipitins At first they developed the supposition that the exanthemata might be produced by mechanical difficulties in circulation, created by the formation of a precipitation brought about by the contact of precipitin with the still present horse serum at the moment that the precipitins enter the blood However they dropped this idea because *Rostoski*, *Michaelis*, and *Oppenheimer* proved that no precipitation takes place in the blood of living organisms

Lately (Soc med des Hopitaux **26:** 5, 1905) *Widal* and *Rostaine* collected experiences from therapeutical experiments in cases of paroxysmal hemoglobinuria, which confirmed the animal experiments of the above named authors also for human organisms

Widal and Rostaine injected anti human serum of rabbits and horses, which gave abundant precipitation in the test tube subcutaneously and intravenously If coagulation would occur in the living animal or human being we would surely see very severe symptoms of sickness brought about by the plugging of capillaries However the individuals behaved as if plain rabbit or horse serum had been injected The first injection showed no immediate reaction excepting in one case where a generalized urticaria developed Only if the injection was repeated local reactions occurred which were similar to the reaction which we observed after the reinjection of normal horse serum As we shall see later it is not simple to show a causal connection between precipitin formation and serum sickness In most cases precipitin appear much later than the disease and even very intensive serum sickness symptoms run their course without the formation of precipitin

Time of Appearance of Precipitin

The precipitins do not appear immediately after the injection of a foreign serum but only after a longer interval, in some measure varying according to the kind of animal and serum used

[illegible]

course of [illegible] the following [illegible]

period o[illegible] he rise of the content of pre-

cipitin 3 [illegible] The drop in antibody content

The second period lasts about two days, the third and fourth periods vary in their duration

After rabbits are injected subcutaneously with horse serum, the period of latency is somewhat longer When five rabbits were injected with 1/100 of their body weight of horse serum, the precipitin appeared in two animals on the seventh day, in three animals on the ninth day (Hamburger and Pirquet) In one rabbit, which received 1/300 of its body weight, the

precipitin did not appear until the tenth day This delay is not the con sequence of the smaller dose but of an individual difference, because in other cases the incubation time is independent of the amount of serum injected (v Dungern)

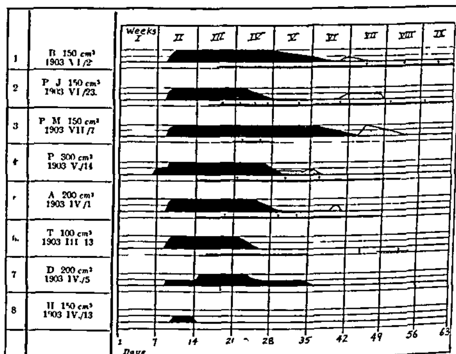


CHART XXXII Serum sickness and precipitation

The black area signifies the time of appearance of distinct serum symptoms (fever, rash, etc) indistinct final symptoms are illustrated by points

Each examination of the children s serum is marked + or −, according to whether or not they showed a precipitate with horse serum The positive results are con nected with a black line

In cases 6 and 7, I means the reinjection of 1 cc serum (immunization against diphtheria) In case 6 the reappearance of precipitin is observed already on the eighth day after reinjection

Human beings do not produce detectable precipitin against horse serum as easily as rabbits do Even doses of 200 cc do not always bring about a detectable formation of precipitin In a number of children investigated for this purpose, it was mostly at the end of the third week that precipitin was found

Our investigation was made microscopically and by mixing children s serum with equal parts of concentrated horse serum Hamburger and also Francioni found precipitin even earlier than the third week This differ

ence may be due either to the method used or to the amount of serum injected Further investigation will decide this question

In human beings the precipitin can be observed for varying lengths of time in case 1 the curve in the chart showed a strong precipitin still in the ninth week, whereas in case 3, after a short presence, no precipitin could be observed already in the fourth week

How now do these antibodies, visible in vitro, behave after reinjection? Here we can distinguish 3 possibilities First the injection during the incubation time, second during the stage of free antibodies, third after the disappearance of the precipitin

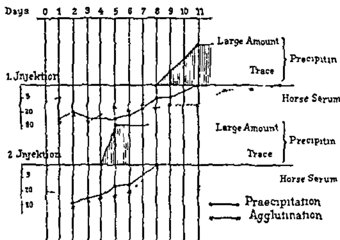


CHART XXXIII

1 The curve of the precipitins is not essentially influenced by the injection of foreign protein during the incubation period 2 If the new injection of foreign protein occurs during the stage of free antibodies, the amount of precipitin drops rapidly immediately after the injection (v Dungern, p 88) The intensity of this drop depends upon the amount of the newly injected serum However, new formation of precipitin takes place during the following days, a formation which considerably passes the original height of the precipitin content This new formation already occurs after a short incubation time

3 When the injection is made after the disappearance of precipitin from the serum of the previously injected animals, the antibodies appear not only in an increased amount, but also markedly more quickly than the first time (accelerated reactivity)

Von Dungern shows several curves of such reinjected animals, which

demonstrate that after an intravenous reinjection, the antibodies already appear after three days

Hamburger and von Pirquet confirmed these findings in rabbits injected with horse serum A characteristic example is the following

Chart XXXIII According to the illustration of v Dungern, the precipitin is marked above the base line, below this line the horse serum detectable in rabbits

The rabbit received at the first injection (on Feb 25, 1903) 6 cc, about 1/300 of its body weight agglutinating scarlet fever streptococci serum Moser

On the days immediately following, only horse serum was in the rabbit's serum, no precipitin was detectable The horse serum was determined by agglutination and also by precipitation through rabbit antihorse serum The precipitation and agglutination of streptococci could still be found with rabbit serum diluted sixty times

The precipitin appears for the first time on the ninth day, does not become abundant until the eleventh day

The second injection was made with the same amount of serum on March 18, 1903, twenty one days later At this time no precipitin was present any more On the fifth day it appeared suddenly in a large amount

Corresponding to the more rapid appearance of the precipitins, the precipitable substance (F Hamburger) and the agglutinine disappeared more rapidly after the second injection

Clinical Symptoms of Serum Sickness as Expression of the Vital Antibody Reaction

Besides the formation of precipitin, after an injection of foreign protein we see another form of reaction in human beings, serum sickness *This is* seen also in animals, but less distinctly

After the first injection, serum sickness appears after an 8 to 13 day incubation period If the injection of the same foreign serum is repeated after a longer interval the reaction appears more rapidly as have been fully described in the preceding chapters The incubation period is shortened to 5 days We called this reaction "accelerated reaction" The disease follows the same law as the formation of antibodies in vitro

We therefore state the theory that there exists a causal connection between the formation of antibodies and disease, whereby we stress the point that we do not identify the term antibody with precipitin, on the contrary we give the term antibody a much wider meaning Only as an external, provable sign of the alteration going on inside the body is the course of the curve of precipitin of value to us The more we place the clinical symptoms into the foreground the clearer it becomes that the

vital reaction demonstrates more sensitively the changes occurring in the organism than the experiment in vitro

In the clinical picture of reinjection we learned not only the accelerated reaction but we were able to prove that at a certain interval after the first injection (12 days to about 6 months) a peculiar form of reaction appears, which we called "immediate reaction" and which we sharply distinguished from the accelerated reaction

If foreign serum is injected subcutaneously within this time, a local edema is formed, which in the most intensive cases increases within 24 hours to 200 times the quantity of injected fluid Besides this and at the same time general symptoms set in, which correspond to the symptoms we are accustomed to see in normally timed serum sickness urticaria, fever, edema lymph gland swelling, joint pains

From the identity of the symptoms we must conclude that the exciting cause for both series of symptoms must be the same If we have shown that the accelerated reaction is connected with the formation of antibodies, so we must also hold the antibodies responsible for the immediate reaction

A new formation of antibodies in the sometimes minimal time between the injection of antigen and the eruption of symptoms cannot be accepted We must therefore assume that the immediate reaction is due to existing antibodies The limitation of the immediate reactivity to a certain period after the first injection (12 days to 6 months) is in full accord with this supposition

That the precipitin disappears sooner than the immediate reactivity can be explained in that the vital reaction is much more sensitive than the experiment in vitro

The immediate reaction throws light upon the mechanism of the serum sickness Until now one could have had the conception that the formation of antibodies as such was combined with the serum symptoms, the serum would be in this case only the releasing stimulus for the formation of antibodies

But in the immediate reaction we see that the antigen plays an important part in the production of the symptoms of the disease It shows definitely that the meeting of antigen with antibodies elicits the symptoms

In a certain respect the immediate reaction can be compared with what is happening in vitro In the stage of free antibodies the organism gives on one hand precipitin reaction on the other hand immediate reaction

We should not forget that the chemistry of the formation of a precipitation is just as unexplained as the mechanism of the appearance of the exanthema We know only the condition under which the reactions appear

Just as a precipitation occurs when we add in vitro one drop of horse serum to the serum containing antibodies, [illegible] edema (the

immediate reaction) develops when an individual possessing antibodies is injected with horse serum The reaction in vivo is just as specific as the reaction in vitro

Are the antibodies of the vital reaction identical with the precipitins? We shall see later (page 108) that in experiments with rabbits a discrepancy exists in the intensity between the sickness symptoms in reinjected persons and the formation of precipitin, likewise these discrepancies are illustrated by the results of experiments with human beings (Chart XXXII)

Case 3, who exhibited the most intensive symptoms of the disease, showed only traces of precipitin during the course of a five weeks' sickness whereas in contrast case 6 with symptoms of medium intensity and of short duration a strong formation of precipitin In case 7 and 8 no precipitin was formed at all Also in cases with strong formation of precipitin the onset of the disease does not coincide with the presence of precipitin The same discrepancy exists in the termination of the disease

Francioni studied the relation of the formation of precipitin and serum sickness in many children In 17 cases he found formation of precipitin at the same time as the appearance of serum symptoms, in 4 cases precipitin formation without disease and in 7 cases serum disease without precipitin formation *Marfan*, to whom we shall come back later, also found no complete congruity between precipitin formation and hypersensitivity in human beings

These findings indicate that antibodies of the vital reaction are not to be identified with the precipitin We know from the various processes of immunization that the same substance creates the production of different kinds of discernible antibodies So for example with an injection of a culture of typhoid bacilli, besides antitoxin also agglutinines and bacteriolytic substances (antibodies) are formed, and their appearance and intensity do not necessarily parallel each other

In general one may say that the vital reaction is more sensitive than the reaction in vitro, particularly as to that which appertains to the duration of the reactivity The precipitin regularly disappears 5–9 weeks after the first injection The immediate reactivity persists for several months and disappears only after ½ or ¾ of a year Even after 1½ years it may be still present as the following case shows

Dr v P was several times previously injected, the last time on 3/16/03 Reinjection on 1/21/05 No trace of precipitin in the blood 15 cc antitetanus serum Within a few hours very intensive specific local reaction No new formation of precipitin

The vital reaction after reinjection is specific

Proof for this is the following

1 Persons injected for the first time never develop the characteristic, extremely intensive local edema after a small dose of serum

A very small local reaction consisting of redness and a little swelling occurs at a first injection, this finding does not destroy the value of the positive reaction just as an insignificant precipitation between sera, which have no antigen relation, does not destroy it

2 The reaction is specific for the antigen in question The experiments relating to this, which we shall report on page 108, were performed only on rabbits—not on human beings Previous injection of horse serum produces sensitiveness only to horse serum, pig serum only to pig serum

That it is a specific reaction to horse serum and has nothing to do with the antitoxin content, can be concluded from the fact that all antitoxic sera, in so far as they are taken from the horse, show amongst themselves the vital reaction In our experiments we used promiscuously diphtheria, scarlet fever, tetanus and normal horse serum (Chart pages 80 and 81)

The essential point of our theory is that the immediate reaction and the sensitiveness after reinjection are a vital antibody reaction

But the antibodies, which are responsible for the reaction, are not identical with the precipitins [illegible]
in the organism which [illegible]
chemical interaction be[illegible]
vital reaction

Let us now return to the explanation of the serum sickness after the first injection In it we see the appearance of sickness symptoms only after 8–12 days The antigen needed for the reaction is present, what is missing is the second agens needed for the reaction—the antibody According to the commonly accepted theory, the latter is formed by the stimulation [illegible]

and tissues of the organism, in a way similar to that of an immediate reaction [illegible]

decided [illegible]

that the first symptoms of a normally timed reaction are very frequently seen at the place of injection Already in 1903 *J Herzka* explained this local reaction as an effect of locally formed antibodies

The accelerated reaction differs from the normally timed reaction in that the antibodies are reproduced more quickly and therefore the disease starts earlier The clinical observation of the accelerated reaction shows another analogy between antibody formation and disease As the curve of precipitin after reinjection not only starts after a shorter incubation time but also rises more steeply and to a higher point, so the accelerated serum sickness starts not only more quickly but also more stormy

Acquired Hypersensitiveness

On this basis a further characteristic sign of the immediate reaction can be understood, i e hypersensitiveness

Whereas after the first injection of even a quantity of 200 cc serum there are often no visible symptoms of serum sickness yet in the case of reinjection in the stage of immediate reactivity as little as 1 cc almost always produces a distinct edema and frequently generalized symptoms

In order to explain hypersensitiveness we must at first get an idea as to what factors are responsible for the intensity of serum sickness

In the clinical picture of the first serum sickness we stated that the percentage of clinically manifest consequences of a serum injection depends upon the kind and the amount of injected serum and upon the individual's disposition How can we bring these facts into accord with our theory?

For the moment we can disregard the part played by the kind of serum as we always used horse serum in human beings, and in the experimental studies we always used the same serum for the first injection as we did for the reinjection

Therefore the only factors which remain are the amount of the antigen and the individual disposition The first factor can be excluded by using the same amount of serum for the first injection as for the reinjection The second factor, the individual disposition, may be based, on the one side, on a different intensity of antibody formation or on the other side on the difference in sensitiveness of the organism to the toxin created by the interaction between antigen and antibody

vice at an interval of 29 days, received The first time there was no reaction, the second time an immediate mild formation of edema

Here the kind and amount of serum are the same We can assume that the individual remained uniformly sensitive to the toxic substance as such For an explanation of the difference in reaction we have only the

absolute amount of toxic substance This depends upon the amount of the substances which interact at the time of the reaction

The second reaction starts immediately after the injection of the foreign serum because the foreign serum can be broken down by the existing antibodies The total amount of antigen can be at one time converted to a toxic substance

Why does not serum sickness develop the first time?

We must assume that in spite of the absence of clinical symptoms, also in this case antibodies entered the circulation about 8–12 days after the injection During the long time until this happens the concentration of antigen has diminished by its distribution throughout the whole body In a diluted solution reactions are slowed down The formation of the toxic substance does not take place with one stroke but is distributed over a longer period of time Thus its effect does not reach the threshold of clinical detectibility

Animal Experiments

In the light of these clinical experiences the result of the animal experiments becomes easily understood—in animals the first injection regularly leads to no clinical symptoms Only after repeated injections at certain time intervals, are immediate reactions observed which after subcutaneous injections vary from local edema to gangrene, after intravenous injection from symptoms of collapse to acute death

Similar experiments were performed by *Arthus*—following the investigations with actinia poison by *Richet*—and were published at about the same time as our first report (Arthus on June 16th, we on June 25th, 1903)

Arthus reports no damage after the first injection of horse serum into rabbits and it was immaterial whether the horse serum was injected subcutaneously or intravenously However if the injections are repeated every six days after about the fourth subcutaneous reinjection local symptoms develop at the site of injection, these symptoms becoming always more intensive, from a simple edematous infiltration to gangrene These local symptoms are not the effect of repeated injections at the same place, as they also appear if the first injection is made intraperitoneally and the new injection is made for the first time subcutaneously

These symptoms are also not the effect of a summation of the serum in the organism of the rabbit, as a large quantity at once or several days in succession does not produce symptoms After an intravenous or intraperitoneal reinjection much more serious symptoms appeared

A rabbit pretreated with 8 injections received 2 cc serum into the earvein Approximately one minute later the animal made movements like sneezing, became anxious and restless, lay down on its abdomen, the

breathing became rapid but not dyspneic (200–250 respirations). Many bowel movements set in, then the rabbit lay on *its side, turned the head* back, made running movements with the paws and finally remained motionless, respiration stopped. After a short pause, when exophthalmus developed in the eyes by extinguished corneal reflexes, the rabbit made 4–5 respirations and died approximately 4 minutes after the injection.

In other cases all the mentioned symptoms disappear in about 15 minutes, the animal seems to be entirely restored to health, but afterwards the animal becomes cachectic. *Arthus* observed similar symptoms after repeated injections of skimmed milk sterilized by 100°C. He concluded from this that all liquid protein substances produce a *condition of "Hypersensitiveness."*

Arthus also knew that after repeated serum injections, human beings develop "a more or less edematous swelling of the area of *injection*." In several points our conceptions differ markedly from Arthus, although we agree with his objective results.

Arthus believes the first injection has no clinical consequences ("Le serum de cheval n'est pas toxique pour le lapin") and after reinjection sees only hypersensitiveness, he overlooked the serum sickness after the first injection, and therefore the difference in incubation time between the first injection and the reinjection remained unknown to him. On this difference we built our theoretical conception.

In contrast to human beings it is difficult to judge the serum sickness after the first injection in rabbits. Moreover Arthus made the possibility of its observation difficult because without waiting for the sickness, he reinjected 5 cc. serum (each time) at regular intervals of 6 days. When he then observed local symptoms from the fourth injection on, which were always missing after the previous injections, it is easy to understand that he laid the emphasis upon the repetition and the total number of injections and not upon the time interval between the first injection and those which produced the local symptoms. Characteristic of this conception is the fact that he calculates the appearance of hypersensitiveness not according to days but according to the number of injections.

In contrast to this we were able to prove that even one single injection creates hypersensitiveness.

From a comparison of our investigations with those of Arthus it can be shown that only the intensity of the specific reaction is increased by frequent repetition of the injections whereas for the time element of the immediate reaction one previous injection suffices.

Experiment to study the onset and duration of the local sensitiveness

rabbit A, the third rabbit C was injected 15 days after A, D 20 days after A E Finally 25 days after A F

On the 30th day after the injection of the first rabbit, all animals each received simultaneously with the control animal 10 cc of the same horse serum into the skin of the abdomen The control animal had had no previous injection of horse serum During the hours immediately following the injection, the control animal showed a soft swelling corresponding to the amount of injected serum This swelling decreased substantially within 24 hours In contrast to this, E developed a hard, intensive infiltration in the area of injection considerably surpassing the amount of injected serum The infiltration was, as Arthus had already pointed out, sterile and persisted for several days

Animals B and C developed less intensive infiltration (Interval 25, 20 days) F & D behaved like the control animal

We see that also in rabbits one single injection is able to create sensitiveness It is not yet present after 5 days, after a 10 day interval it is clearly established Immediately before reinjection, the animals were examined for the presence of precipitin, with regard to the connection between precipitin formation and local reaction The strength of the precipitin formation does not correspond to the intensity of the local reaction The animal with a 20 day interval did indeed show a strong local reaction combined with a strong formation of precipitin, the animal with a 5 day interval no local reaction combined with the existence of a trace of precipitin, in contrast the animal with a 25 day interval showed a strong local reaction, without finding precipitin in the blood Traces of precipitable substances were found in all cases A further blood examination was made 7 days after reinjection The repeatedly injected animals showed a formation of precipitin almost twice as strong as the control animal, a proof that after reinjection the antibodies appear earlier and in a greater amount

The Specific Edema

Whereas we could describe many symptoms of serum sickness in human beings, rabbits show almost no symptoms outside of the local reaction Therefore the significance of this symptom is pushed into the foreground

We use the outside of the earlobe as a suitable place for reinjecting the rabbit It has the advantage over the abdominal skin of being easier to watch An example will show how easily observation can be made at this place

Rabbit 68, preinjected on 12/12/03 with 10 cc horse serum in the abdominal wall In the afternoon of 1/4 (23 days later) a reinjection of 5 cc into the right ear In morning of the next day no striking swelling, in the afternoon and increasing for 3 days a tremendous erysipelas like infiltration of the ear The ear is hot and thick, hangs down As mentioned before, the skin of the forearm is the most suitable area for observing a reinjection in human beings

Arthus furthermore proved that the vital local reaction is a specific one Cow milk creates sensitiveness only to cow's milk, horse serum only to horse serum We could also prove that the reaction is specific, using horse serum and pig serum for the pretreatment of rabbits When the injection was repeated, specific edema appeared at the place where the same antigen was injected the second time

Experiments

Also in human beings frequently enough symptoms appear only at the site of injection which can exhibit either merely a specific edema with a pale skin or we find it at the same time a mottled or urticarial eruption appears or erysipelas like redness in the edematous skin Just as these

First injection on 3/4/05, second injection on 3/15/05 (after 11 days)

Rabbit no	Weight	First injection abdominal skin	Reinjection (ear)			
			Right	Edema	Left	Edema
12	2710	13 cc pig serum	3 cc horse serum	0	—	—
69	2210	11 cc pig serum	—	—	3 cc pig serum	++
321	2530	12 cc pig serum	3	0	3	
92	3150	15 cc horse serum	3	++	—	—
431	3000	15 cc horse serum	—	—	3	0
102	2960	15 cc horse serum	3	++	3	+

local eruptions are analogous to the generalized eruptions of persons injected for the first time and of reinjected persons, so we put this local edema in the same category as the general edema, which accompanies the general rash of persons injected for the first time

The local edema cannot be determined by a scale but by replacement of water or by measuring (See p 84)

We saw, as we reported before, local edema in which the amount of injected serum produced a 50 to 200 times larger swelling In a reaction at normal time we find a similar relation between the amount of injected serum and the universal swelling due to this serum

After an injection of 10 cc diphtheria serum in Rudolf B a universal edema develops accompanied by urticaria, the amount of which was determined, by weighing, to be 1100 grams The relation of edema to the amount of injected serum is 1:100 (Chart II)

The discrepancy in the proportion between the amount of antigen and edema was already pointed out on page 84 It is also valid for the edema of serum sickness at normal time

Thus Karl A (page 45) had 2000 gram edema after an injection of 200 cc serum, Franz K (page 41) with the same dose only 400 gram In many cases (Otto D, p 37) we are not even able clinically to determine the edema by weighing Chart XIII p 37

The great difference in various individuals in the formation of edema, with respect to local as well as universal edema, indicates that the edema is not to be conceived as a physical phenomenon which accompanies the interaction between precipitate substance and precipitin, but as an end effect of a toxic stimulus, through which the individual disposition is afforded larger room for action

That it is the interaction between horse serum and antibodies which creates the toxic substance we further tried to confirm by creating artificially the condition for the reaction in an animal not previously injected

These rabbits each received 10 cc horse serum in the abdominal wall After 24 hours, when resorption can be assumed to be finished, but an active antibody could not be expected to be present, two rabbits each received 2 cc anti horse serum prepared from rabbits, one rabbit received 2 cc in the ear lobe Whereas the last showed no reaction at all, one of the first two rabbits showed a typical reaction (edema), the other slight edema of the ear

Numerous experiments in order to produce specific edema have not given clear results These experiments consisted of injecting a mixture of horse serum with anti horse serum or of simultaneous injection of both substances, finally injecting with horse serum after having previously treated with anti horse serum

Acquired Immunity, Hyposensitiveness and Lack of Sensitiveness

A closely related question is whether the organism retains the hypersensitiveness after repeated injection of foreign serum, or whether the hypersensitiveness changes to a condition of clinical immunity as it happens with tuberculin

The results of animal experiments apparently are decidedly against this conception Animals repeatedly reinjected at intervals of 6–10 days react always more intensively with severe local reactions and after some time become marasmic and die

From this *Wolff* drew the conclusion that serum differs in principle from those substances, against which true antitoxin is formed, and brought the serum in analogy to the endotoxins The experiences made with eel serum also are against the mentioned theory and in favor of the existence of true immunity in these processes As early as 1902 *Hamburger* studied this question He injected egg white into animals and used the excretion albumen in the urine as an indication of immunity He found that the

albuminuria, which was otherwise always observed after an injection of egg white, disappeared His experiments did not remain unopposed Our experience with humans does not permit us to make a definite decision

Dr v P First injection in the spring of 1902 200 cc scarlet fever serum, serum sickness sets in after 8 days and lasts one week

2nd injection, 2/11/03 1 5 cc diphtheria serum (interval 9 months) after half an hour itching after one hour slight red swelling of 1 cm radius

3rd injection 2/21/03 (interval 10 days) 8 cc diphtheria serum *Mild specific edema* described on page 84

4th injection 2/27 (interval 6 days) 6 cc diphtheria serum Slight swelling

5th injection 3/5 (interval 6 days) 3 cc diphtheria serum Hardly perceptible swelling

6th injection 3/16 (interval 9 days) 9 cc diphtheria serum Slight swelling

The first injection ran a typical course Incubation time of 8 days, that is normally timed serum sickness Nine months later after an injection of a small amount of serum a minimal, not positively specific, reaction Through this injection the sensitiveness seems to have been reawakened because when ten days later a large amount was injected a specific local reaction appeared

It is significant that through this repeated injection the sensitiveness appeared more quickly than after the single injection, when we do not see it until the third week It may be that this is to be explained by the accelerated new formation of antibodies The next injections seem to confirm the assumption that the organism became hyposensitive to the serum—that is, became immune

But it is difficult to bring the result of the seventh injection into accord with this statement

Dr v P 1/21/05 (interval 22 months) Injection of 15 cc antitetanus serum Strong specific edema, described on page 83

The result is neither in accord with the supposition of an increasing immunity nor with the regular behavior of the reaction period—according to chart XXXVIII, which established that at intervals of more than 9 months the immediate reaction is replaced by an accelerated reaction

To be sure, only cases with one previous injection were used in this chart and it is possible that local sensitiveness lasts longer due to *many rein*jections and large doses

Johanna Cz 13 years admitted on account of malignant diphtheria For therapeutic purposes repeated injections of diphtheria serum in short succession

Up to this point no symptoms of serum sickness appeared We are within the normal time incubation where sensitiveness is not yet established From very many reinjections during the first days we learned that repeated injections during the normal incubation time never bring about an earlier appearance of the disease All doses are summarized for one single reaction which turns out as if the total dose had been given at once on the first day This reminds us of the behavior of smallpox vaccination, where those areas which have been revaccinated during the incubation period reach the full reaction at the same time as the primary vaccination reaction (Sobotka et al)

In the aforementioned case the sickness in accordance to this law appeared 10 days after the first injection in the form of a general rash While the serum symptoms were still present the sixth injection on 4/3 (interval 13 days) 3 cc were given In the afternoon generalized urticaria, joint pains

Seventh injection 4/6 (interval 16 days) 3 cc In the afternoon 38 2°, morbilli like eruption in the skin of the epigastrium, confluent rash Pain in the hand on 4/7 and 4/8 fever, joint pain On 4/9 no fever

Eighth injection 4/11 (interval 21 days, 3 cc) Half an hour after the injection edema at the area of injection Urticarial zone on the skin of the epigastrium Scattered urticaria over the entire body

Ninth injection 4/17 interval 27 days 3 cc serum Immediately after the injection a local eruption of a rash

In spite of the numerous injections this case is not very suitable for answering the question whether or not an immunity against serum develops The first five injections fall into the incubation period and sum up to one single reaction, which with several new eruptions lasts for one week Therefore it is not possible to judge the effect of the sixth and seventh injections which fall into the reaction period Only the eighth injection is undoubtedly followed by a specific immediate reaction, proven by the local edema This edema appears here for the first time after an interval of 21 days Only a comparison of the intensity of the two last reactions

reaction than the previous one

From the following case one could conjecture the possibility of tolerance

Johann G , also repeatedly reinjected on account of malignant diphtheria Whether in former years an injection had been given could not be ascertained

2/7/03 3000 A U 18 cc serum On 2/12 (6 day) in the forenoon

Observation 2nd, 3rd and 4th injections

insufficient in the skin of the arm Afternoon the area of injection slightly edematous, a little painful

5th injection 2/27 interval 20 days 4 cc After half an hour the area of injection red 24 hours later slightly infiltrated

6th injection 3/2 interval 23 days 3 cc injected Soon afterwards, limited swelling around the site of injection 24 hours later no reaction

7th injection 3/5 interval 26 days 3 cc No reaction well observed

8th injection 3/8 interval 29 days 3 cc No reaction well observed

9th injection 3/16 interval 37 days 3 cc No reaction well observed

The child developed a positively established serum sickness, and after his clinical termination received eight more serum injections It cannot be stated whether a local reaction took place after the first two injections (2nd and 3d) However it is certain that after the 4th, 5th, and 6th specific edema developed and that later the reactivity diminished

Lately *Marfan** influenced by *Arthus* published many observations concerning hypersensitiveness to serum

He reports six cases of immediate reaction

The first case in which the first rash appeared after 5 days and the violent symptoms terminated after 2 days showed a great amount of precipitin as early as 8 days after the injection

Judging from the rapid appearance of all symptoms it seems probable that the child had been previously injected and shows an accelerated reaction

This is also in accord with the observation that when reinjected after an interval of ten days immediate, specific edema developed

Case 6 shows the peculiarity that no specific edema developed in spite of the presence of a weak precipitin reaction

The accelerated reaction was unknown to Marfan and Le Play which was probably connected with the fact that in the selected interval (10–32 days) the immediate reaction is the rule and a later appearing *accelerated* reaction the exception

The following cases of Marfan and Le Play are valuable for the consideration of immunity Case IV First injection 10/15/04 20 cc diphtheria serum After 6 days generalized urticaria, 39 3° temperature After 9 days weak precipitin reaction 2nd injection, interval 14 days 5 cc specific edema, 38 9°, strong precipitation 3d injection, 19 days after the first injection 5 cc specific edema, precipitation 4th injection, 23 days after the first injection 5 cc slight swelling, weak precipitation 5th injection, 31 days after the first injection 10 cc no edema but on the following day mild urticaria, weak precipitation 6th injection, 40 days after the first

* Marfan and LePlay, Rechérches sur la pathogenie des accidents serothérapiques (Soc med des Hôpitaux 3/24, 1905)

injection 5 cc Very little edema, very weak precipitation Here the local reaction decreased visibly during the course of the first month It would have been very interesting if the entire course of the repeated injections in case VII could have been observed

A six year old girl, being a difficult case of decanulement was a patient in the diphtheria ward for almost three years, received each month or every second month 5 cc diphtheria serum for passive immunization

On July 15, 1904 Marfan demonstrated the girl at a meeting of the medical society as a proof that the observations of Arthus are not valid

First injection (cc)	30	50	40	20	40	60
Incubation time and kind of serum symptoms after first injection	5 day urtic joint pain 39 8°	8 days urtic 39 1°	8 days erythem	6 days urtic 39 3°	11 days urtic	9 days urtic
Interval	10 days	11 days	32 days	14 days	17 days	12 days
Amount of serum at the second injection in cc	5	5	20	5	5	5
Reaction	edema lymph gl swelling		gen urtic 39	edema	edema	no edema
Precipitin reaction	++	++	+	+	++	+

for human beings Up to that time the girl had received 24 injections without any symptoms being noticed after the injections

It is peculiar that from now on the findings changed The 27th and 28th injection were followed by local edema and slight fever In any case it is interesting that the sensitiveness still exists after so many injections of serum

That no precipitin was found after the 25th and 27th injections would have been an important phenomenon, if the experiments had been repeated several times But it was done 0, 1 and two days after the injection It could be possible that precipitin was formed each time more rapidly but would perhaps appear only on the 4th to 6th day That no precipitin was found during the first days is no proof that it is not formed at all

The Importance of Serum Sickness in General Pathology

We consider the discovery of the immediate and accelerated reactivity in serum sickness as the two most outstanding results of our investigations Before us both forms of reaction had been overlooked Only the hyper sensitiveness which accompanied the immediate reactivity in various antigens was already dealt with by other authors

It was only Arthus who, simultaneously with us, described the hyper sensitivity in serum sickness and realized its importance He proceeded from the investigations of *Richet* who observed in experiments with actinia venom that the lethal dose for a dog is 0 1–0 18 grams per kg body weight, when the dog is injected for the first time Death never occurred earlier than 10 hours after the injection In case of reinjection—the injection of the poison was given intravenously—the animals died in the first place after smaller doses (0 15 g was always fatal) and in the second place more quickly The following is a characteristic example

For its first injection a dog receives 0 10 actinia venom per kg body weight, after which there were no distinct symptoms

Twenty two days later another injection of 0 10 g pro kg was made into the vena saphena, after a few seconds the respiration became labored The dog can hardly move around any more, lies down on its side, has diarrhea and hemorrhagic vomiting, dies after 25 minutes (C Portier and Ch Richet, Bull de la soc d biolg, 1902 p 170, Ch Richet Arch di Fisiologia, 1904, p 129, and Soc d bil, Jan 21st 1905)

Richet extracted two different substances from the actinia poison the crystalline *thalassin* which is only slightly toxic, but which already in minimal doses produces pruritus, and the albumen *kongestin*, which by far surpasses the original poison in toxic effect and which produces the characteristic congestive conditions in the digestive tract *Richet* made further experiments with *kongestin* which as far as the relation of the first injection and the reinjection are concerned, gave the same results as the experiments with the actinia poison The lethal dose for the rabbit when injected the first time is 0 009 per kg, when reinjected it is less than 0 0033 g

Richet coined the term *ana*-phylactic effect for the results of the first injection which produces hypersensitiveness The term was selected to express the difference from a *pro*-phylactic effect

Anaphylaxis (hypersensitiveness) needs a certain amount of time for its development (hypersensitiveness is not yet present three to four days after the first injection) It persists for a long time and after one year is still distinct Transference of hypersensitiveness by means of serum of injected animals into another animal was not successful *Richet* quotes similar observations with tuberculin and tetanus

Knorr, *Behring* and *Kitashima* reported that guinea pigs show an increasing sensitiveness to repeated injections of tetanus toxin (Experimental investigations about the limitation of curability of tetanus, V, 1902, 18, Berliner klin Wochenschr, 1901, p 157)

Richet believes that in separating the two substances—thalassin and congestin—from the actinia venom—he had found the representative of the venom, the congestin causes the anaphylactic effect, the thalassin the prophylactic The congestin produces hypersensitiveness, thalassin leads to immunity

From these experiments it may be concluded that the Congestin possesses anaphylactic effect in a high degree However the proof does not seem convincing that congestin could not act also as an immunizing substance and on the other hand thalassin as an anaphylactic substance Moreover it is unlikely that such a separation of opposite substances could be carried out similarly in other material with anaphylactic effect as horse serum tetanus toxin or tuberculin

The results of Richet s experiments can be explained with the assumption that the congestin is the more toxic and the thalassin the less toxic part, and therefore the prophylactic effect of thalassin can become apparent as an immunization with attenuated cultures and poisonous substances Serum and actinia venom are similar in the respect that both are substances which are unable to multiply However there is an important difference between them inasmuch as the actinia venom acts after the first injection without an incubation period whereas even a large amount of serum almost never produces symptoms immediately following the first injection

As far as the serum is concerned, we could prove that it is as such not toxic, but that the toxic substance is created by the interaction between the organism and the antigen Other kinds of animal protein like milk (Arthus), spermatozoa (Wolff) behave in a similar way

In spite of this difference in respect to the primary toxicity in both cases the previous injection brings about equal alterations in the organism, characterized clinically by hypersensitiveness It is only the accelerated reaction which can not be observed in substances like actinia venom which are toxic as such, because the integral part of the accelerated reaction (the shortened incubation time) cannot be seen as these poisons produce symptoms without an incubation period

Hypersensitiveness in tuberculosis can be explained in an analogous way to that of actinia venom The behavior of tuberculin is being much more intensively studied, and besides hypersensitiveness there is another principle known namely the transition of this hypersensitiveness to lack of sensitiveness—Immunity

Tuberculin is an extract which is not able to multiply, but originates from a germ which is able to multiply, and we can expect that after an infection with tubercle bacilli, hypersensitiveness may be created in the same way as it is by injecting with extracts or with dead bacilli Thus we reach the discussion of hypersensitiveness in infectious processes

As early as 1888 *Arloing* had expressed his opinion that pathogenic microorganisms, particularly tubercle bacilli, excrete soluble substances, which influence the organism in such a way that the animals die more rapidly if they are later infected with the same bacilli

Courmont studied this problem extensively with tubercle bacilli (Revue médicale, 1891, No 10, p 831, ref Zentralbl f Bact, Vol 13, p 714) Bovine tubercle bacilli, derived in pure culture from a tubercle in the pleura, produces a generalized tuberculosis in rabbits and kills guinea pigs without macroscopically visible alterations *Courmont* injected animals with soluble products derived from tubercle bacilli by filtration of young cultures Guinea pigs and rabbits never react to these injections When animals, so prepared, are immediately afterwards infected with a pure culture, they behave like normal animals

However if the animals were infected several days after they were injected with the soluble products, the results were quite different

If animals, which had been injected with filtrate twenty days ago and since that time felt well, are infected subcutaneously with a tubercle taken from a guinea pig then the guinea pig dies in 15 hours, the rabbit in about 23 hours These animals die sixteen times more quickly than the control animals This predisposition exists in full strength from 4 to 20 days after injection *Courmont* assumed that the organism, by means of the previous injection becomes a more favorable soil for the infection It is exposed defenceless to the infection The essential part of *Courmont's* explanation lies therein, that the organism as such possesses protective substances, which wall off the infection The protective substances are eliminated by the first injection of the mentioned soluble substances This theory which we shall still encounter frequently, we wish to call in short "*Elimination*" theory *Courmont* leaves unexplained why several days are necessary for the elimination

The *Lyonnaise* school attributes these observations to other microorganism such as staphylococci and streptococci, *bacillus pyocyaneus*, etc *Rist* made similar observations with diphtheria bacilli

Strauss and *Gamaleia* report that animals after a second injection of dead tubercle bacilli die suddenly, whereas at the first injection large quantities are tolerated without any reaction Similar results are published by *Babes* and *Proca*

Contrary to the "Addition" theory of *Koch*,—accepted by most German

authors and likewise contrary to the "Elimination" theory of the Lyonnaise school—as early as 1891 *Koehler* and *Westphal* offered a third theory concerning the effect of tuberculin These authors were of the opinion that through the combination of tuberculin with the products of tubercle bacilli in the tuberculous foci, a third substance was formed, which produces the clinical symptoms of the tuberculin reaction

Marmorek (Society de biol 1904) has a similar conception concerning the origin of fever during the tuberculin reaction, he believes that under the influence of tuberculin, the tubercle bacillus may secrete a pyrogen substance

Bail, stimulated by the investigations of *Detre Deutsch*, took up the experiments of Courmont again, and made a careful study of hypersensitiveness in tuberculosis To explain the hypersensitiveness of tubercular guinea pigs to reinfection Bail developed another theory which he

tubercle bacilli, is injected into an animal which had no previous injection, this animal also dies rapidly

Bail imagines that the tubercle bacillus secretes a soluble substance within the organism, which paralyzes the leukocytes He called this substance *agressin*

The exudate obtained after reinjection contains this *agressin* In the experiments of transmission the agressin paralyzes the leukocytes, i e, the protective substance of the new organism The poisonous substance of the tubercle bacillus now rapidly exerts its effect This explanation corresponds, in principle to the "elimination theory" of Arloing and Courmont

During the last year Wolff also studied the problem of hypersensitiveness and developed extensive theoretical considerations based on the investigations of *Pfeiffer* dealing with endotoxins

Endotoxin can only produce its effect when the bacterial covers are dissolved through bacteriolysine, i e, liberated by antibodies As soon as the endotoxin is set free it is immediately poisonous without any incubation time Pfeiffer's and Wolff s theory concerning the method how endotoxin exerts its toxic effect is very closely related to our theory about the nature of serum sickness

Wolff also tried to include in his studies the hypersensitiveness after reinjection of dissolved protein substances, and in this respect based his work on Arthus' and our observations

The theory of the endotoxin, which was liberated by bacteriolysine, cannot be applied to dissolved protein substances We can only accept it

in the sense that by interaction of antibodies and antigen, a toxic substance is formed, but then Wolff has the same viewpoint as we established one and one-half years before him Where bacteriolytic antibodies play a part in bringing about the reaction we must remember that their production sets in only after a certain incubation time

This leads us to the question of the nature of the incubation time, the explanation of which cannot be an uniform one The long incubation period in tetanus was made clear by the fact that, as was proven experimentally, the tetanus toxin has a long way to travel along the nerves until it comes in contact with the cells which are susceptible to the toxin

In malaria it is shown that the interval between two attacks depends upon the fact that only certain phases of the development of the parasite produce symptoms of the disease

A similar conception prevails for a list of other infectious diseases (as measles, variola etc) in which one considers the incubation period as the breeding time of the inciting germ

Samuel (Eulenburg s Realencyklopedia) says "The explanation of the incubation time most likely is that besides the multiplication and migration of the infectious germs, their further development must take place, which in this stage produces the stormy pathological effect "

In Perl's General Pathology edited by Neelson, we find a similar train of thoughts "The easiest way to explain the incubation time is by the supposition that the invading parasite becomes dangerous only after it has reached a certain stage of its development "

In spite of their external differences these theories have in common that they all seek the cause of the incubation time only and exclusively in the causative agens (the germ) and its metabolic products and they do not take in consideration the infected organism

In their explanation of the incubation time in infectious processes Pfeiffer, Wassermann and Wolff pay more attention to the organism

The role played by the organism becomes clear from the circumstance that just as there are laws of reactivity in serum sickness so they are also [illegible] processes

[illegible] ated most beautifully in vac-
[illegible] ner Naturf u Aerzte Kassel,
1903)

Whereas the earliest that the general reaction is seen after a first vaccination is on the seventh day, it always appears decidedly earlier after a revaccination

Also the course *of reaction is* altered in the sense of a considerable shortening and diminution of symptoms The earlier the reaction appears the less intensive is the entire process

How can we explain this finding? According to the earlier conception of incubation time and disease, that the inciting germ must multiply to a threshold of ability to elicit disease, we have to assume that the germ could develop and increase more rapidly in an organism that had been already injected than in an organism that had not been injected We have mentioned that Arloing even expressed this opinion Against this view is the fact that in tuberculosis and vaccination the incubation time is not shortened through an injection of an enormous amount of germs *Beclère Chambon* and *Ménard* have shown that when calves are vaccinated, the disease even then does not appear earlier when the calves are injected with a large amount of vaccination material

The virulence of the germ cannot be responsible because one and the same vaccination material produces after a first vaccination a normally timed reaction, and after a revaccination, an accelerated reaction

In a disease due to a multiplying germ, the law of accelerated and immediate reactivity and sensitiveness is also valid

A related train of ideas regarding infectious diseases can be found in a study about Cure and Immunity written by *Buttersack*, (Virchow's Arch, Vol 142) in which he states that the cure is brought about through inhibition [illegible]

Butt [illegible]

by p [illegible]

bring about this inhibition of development more rapidly in the case of a repeated infection However we wish to explain immediately the essential differences between *Buttersack's theory and ours Buttersack* places the moment of inhibition of the development i e of the action of the organism, at the highest point of the disease, whereas we bring already the beginning of the disease in connection with the antibodies Our conception of anti bodies does not coincide with the usual term of antitoxin, but we use the term in a quite general way as the sum of the specific products of reaction of the organism created by the *introduced antigen*

As an explanation of serum sickness *Buttersack's* theory does not suffice, because in the case of serum, which is a substance not capable of multiplying an inhibition of development cannot take place at all

The conception that the antibodies, which should protect against disease, are also responsible for the disease, sounds at first absurd This has as its basis the fact that we are accustomed *to see in disease only the harm done*

[illegible]

of immunity only by means of disease

Modern medical science seeks to obtain this immunity on the basis of a

mild disease and where possible a disease running a local course In infectious diseases we clearly see the advantage so to speak the teleological significance of the accelerated reaction

The earlier the reaction of the organism ensues (vaccination), the less time has the foreign intruder to multiply, the quicker will its development be inhibited, that much less will be the consequential damage to the whole organism

On the other hand in serum sickness one has the impression that it is unfavorable for the organism to react more quickly after reinjection because the quicker the antibodies interact with the antigen the more intensive will be the disease

This contradiction can perhaps be explained by the fact that an introduction subcutaneously of a non multiplying agens relatively seldom takes place in nature (sting by insects, snakevenom) Serum sickness represents so to speak an unnatural (artificial) form of disease The usual cause of disease is in the vast majority of cases the invasion of small amounts of germs capable of multiplication The defense mechanism of the organism is phylogenetically mobilized in accordance with this form of disease

The accelerated reactivity is the permanent advantage the organism has acquired by having overcome the first disease

Immediately after the termination of the disease the organism is in the stage of free antibodies in consequence of which we observe the immediate reactivity and hypersensitiviness

This phase has only a limited duration The free antibodies disappear, but in spite of it the individual is immune But the essence of this immunity does not lie anymore in the immediate reaction against the infectious germ but in an accelerated reproduction of antibodies

Thereby the organism is placed in a position to wall off the reinfection more quickly, to localize it, as we were best able to recognize it as the result of revaccination

This ability to localize a repeated infection does not rest on the presence

one so perhaps there also exist other kinds of cellular immunity Wassermann's observations about the adaptation of the tissue to a symbiosis with originally pathogenic microorganism, without a detectable antibody reaction point to a different form of immunity based on a lack of sensitiveness

Many diseases, as variola, measles, varicella rubella are characterized by the fact that one triumph over an attack of the disease grants a more or less certain protection for life They have the common clinical peculiarity that after an incubation time that is long regular and independent from

the virulence of the inciting germ, the duration of the disease is very much limited in time

If the organism does not succumb to the disease, so it has completely conquered the infectious agens The latter no longer carries any danger for the organism

The nature of clinical immunity for this group of diseases, as their para digma we regard the vaccination, does not consist of an acquired insensibility towards the infectious germ, but in the ability of an accelerated reaction

With our studies, we endeavored to revive interest in serum sickness and we believe to have shown that this disease has great importance, not only *from a clinical viewpoint but also from the standpoint of general pathology serum sickness is the best paradigma for a disease due to an organic cause which is unable to multiply, and is an exquisite object for the study of the changes going on in the system*

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